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=> d his ful

     (FILE 'HOME' ENTERED AT 11:01:50 ON 08 MAR 2006)

     FILE 'REGISTRY' ENTERED AT 11:01:54 ON 08 MAR 2006
                E MPG/CN
L1            7 SEA ABB=ON  PLU=ON  MPG/CN
                D SCA

     FILE 'HCAPLUS' ENTERED AT 11:02:35 ON 08 MAR 2006
                E US2003-658971/APPS
L2            3 SEA ABB=ON  PLU=ON  (US2003-658971/AP OR US2003-658971/PRN)
                SEL RN

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                BI OR 162990-46-7/BI OR 17460-56-9/BI OR 36215-07-3/BI OR
                667917-13-7/BI OR 667917-14-8/BI OR 667917-16-0/BI OR 667935-30
                -0/BI OR 76-09-5/BI OR 667917-15-9/BI OR 667917-82-0/BI OR
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                I OR 667917-83-1/BI OR 667917-86-4/BI OR 667917-88-6/BI OR
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                864466-85-3/BI OR 864466-86-4/BI OR 864466-91-1/BI OR 864466-92
                -2/BI OR 864466-93-3/BI OR 864466-94-4/BI OR 871575-98-3/BI OR
                871575-99-4/BI OR 871576-00-0/BI OR 871576-01-1/BI OR 871576-02
                -2/BI OR 871576-03-3/BI OR 871576-04-4/BI OR 871576-05-5/BI OR
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                /BI)
L*** DEL      0 S L3 AND MPG
L4           33 SEA ABB=ON  PLU=ON  L3 AND B/ELS

     FILE 'HCAPLUS' ENTERED AT 11:03:55 ON 08 MAR 2006
L5            3 SEA ABB=ON  PLU=ON  L2 AND L4
                D IALL HITSTR 1-3

     FILE 'LREGISTRY' ENTERED AT 11:17:59 ON 08 MAR 2006
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L7            0 SEA SSS SAM L6
L8            0 SEA SSS FUL L6
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L9              STR L6

     FILE 'REGISTRY' ENTERED AT 11:29:14 ON 08 MAR 2006
L10           7 SEA SSS SAM L9
L11         108 SEA SSS FUL L9
L12          21 SEA ABB=ON  PLU=ON  L4 AND L11

     FILE 'HCAPLUS' ENTERED AT 11:29:39 ON 08 MAR 2006
L13          58 SEA ABB=ON  PLU=ON  L11


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:    7 MAR 2006  HIGHEST RN 876109-17-0
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DICTIONARY FILE UPDATES: 7 MAR 2006 HIGHEST RN 876109-17-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

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*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005. A new display format, IDERL, is now      *
* available and contains the CA role and document type information. *
*                                                                    *
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE HCAPLUS

FILE COVERS 1907 - 8 Mar 2006 VOL 144 ISS 11
FILE LAST UPDATED: 7 Mar 2006 (20060307/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE LREGISTRY
LREGISTRY IS A STATIC LEARNING FILE

NEW CAS INFORMATION USE POLICIES, ENTER HELP USAGETERMS FOR DETAILS.

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=> d que stat
L9              STR
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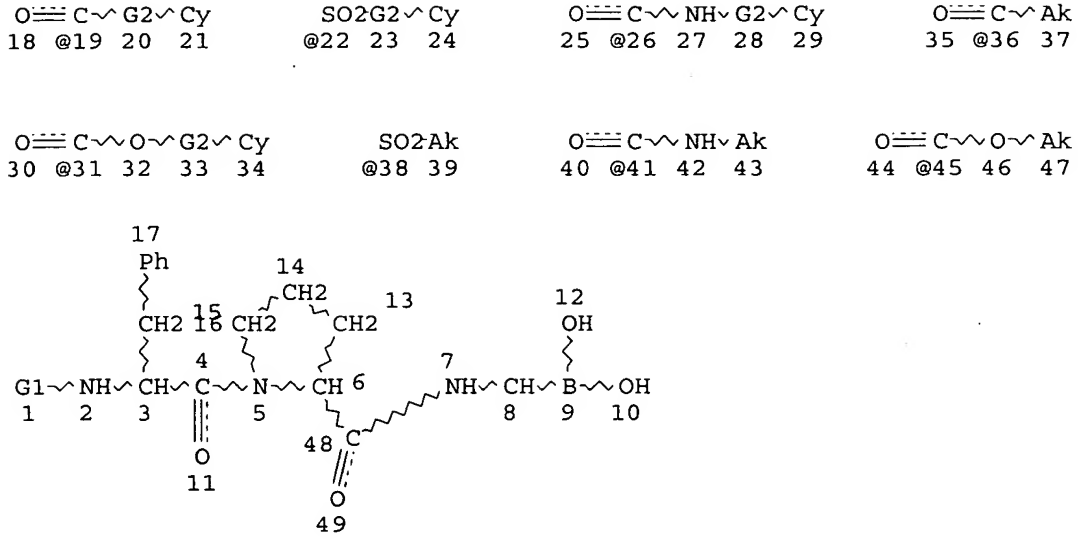

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REP G2=(1-6) CH2
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 49

STEREO ATTRIBUTES: NONE
L11 108 SEA FILE=REGISTRY SSS FUL L9
L13 58 SEA FILE=HCAPLUS ABB=ON PLU=ON L11

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L13 ANSWER 1 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1333982 HCAPLUS
DOCUMENT NUMBER: 144:70109
TITLE: Preparation of peptide boronic acids as anticoagulants
INVENTOR(S): Combe-Marzelle, Sophie Marie; Kennedy, Anthony James; Allen, Graham Douglas; Withington, Roger; Krimmer, Dieter
PATENT ASSIGNEE(S): Trigen Limited, Switz.
SOURCE: U.S. Pat. Appl. Publ., 75 pp., Cont.-in-part of U.S. Ser. No. 937,181.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005282757	A1	20051222	US 2005-78097	20050309
AU 2003263328	A1	20040329	AU 2003-263328	20030909
AU 2003263333	A1	20040329	AU 2003-263333	20030909
AU 2003263343	A1	20040329	AU 2003-263343	20030909
US 2004138175	A1	20040715	US 2003-658971	20030909
US 2004147453	A1	20040729	US 2003-659179	20030909
EP 1466916	A1	20041013	EP 2004-76510	20030909
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
EP 1466917	A1	20041013	EP 2004-76521	20030909
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003014450	A	20050726	BR 2003-14450	20030909
BR 2003014518	A	20050726	BR 2003-14518	20030909
EP 1561466	A2	20050810	EP 2004-76548	20030909
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005288253	A1	20051229	US 2003-659178	20030909
JP 2006503903	T2	20060202	JP 2004-569794	20030909
US 2005119226	A1	20050602	US 2004-937181	20040908
US 2005176651	A1	20050811	US 2004-937854	20040908

PRIORITY APPLN. INFO.:		
GB 2002-20764	A	20020909
GB 2002-20822	A	20020909
GB 2003-7817	A	20030404
GB 2003-11237	A	20030516
GB 2003-15691	A	20030704
US 2003-501718P	P	20030909
US 2003-658971	A2	20030909
US 2003-659178	A2	20030909
US 2003-659179	A2	20030909
US 2004-937181	A2	20040908
US 2004-937854	A2	20040908
US 2003-485786P	P	20030708
EP 2003-255590	A3	20030909
WO 2003-GB3883	W	20030909
WO 2003-GB3887	W	20030909
WO 2003-GB3897	W	20030909

OTHER SOURCE(S): MARPAT 144:70109

AB The invention relates to peptide boronic acids and their pharmaceutically-acceptable salts and prodrugs which are useful for preventing thrombosis where rapid onset and/or rapid offset of anticoagulation is required. The boronic acids have a neutral thrombin P1 domain linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites. Thus, Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)2 (TRI 50c; Cbz = benzyloxycarbonyl; Mpg = 3-methoxypropylglycine residue) and several salts were prepared The activity of TRI 50c magnesium salt in a thrombin amidolytic assay is shown in a figure.

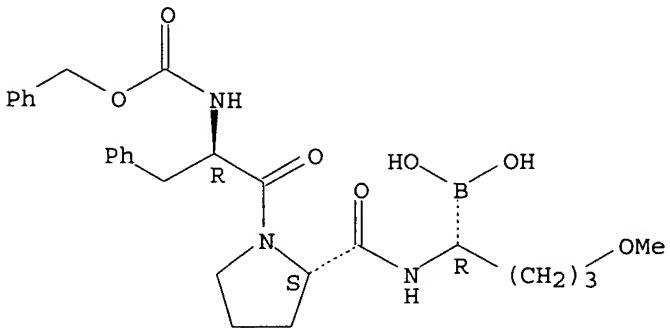
IT **871575-98-3P 871575-99-4P 871576-00-0P**
871576-01-1P 871576-02-2P 871576-04-4P
871576-05-5P 871576-06-6P 871576-08-8P
871576-12-4P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of peptide boronic acids as anticoagulants)

RN 871575-98-3 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-methoxybutyl]-, monosodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

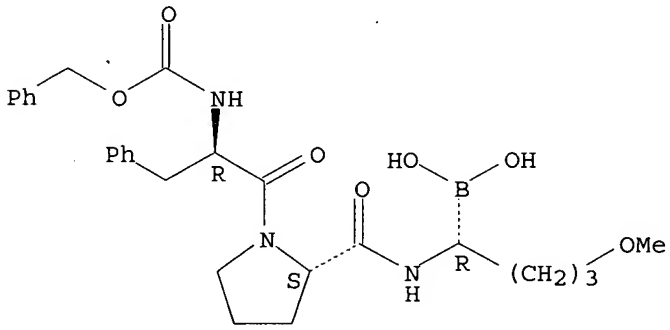


● Na

RN 871575-99-4 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-methoxybutyl]-, calcium salt (2:1) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

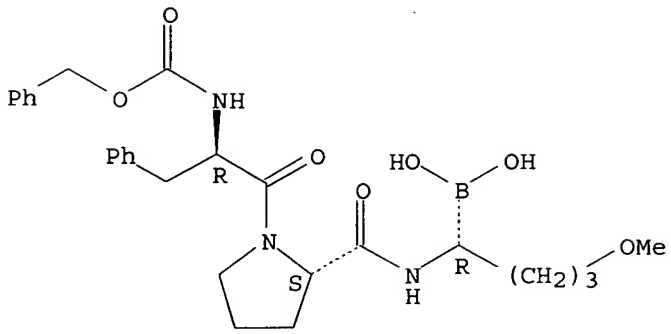


●1/2 Ca

RN 871576-00-0 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-methoxybutyl]-, monolithium salt (9CI) (CA INDEX NAME)

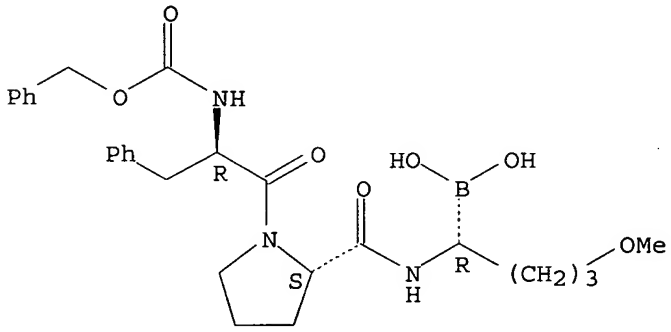
Absolute stereochemistry.



● Li

RN 871576-01-1 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-methoxybutyl]-, monopotassium salt (9CI) (CA INDEX NAME)

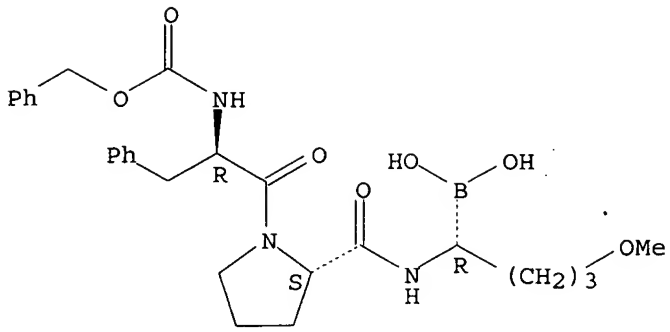
Absolute stereochemistry.



● K

RN 871576-02-2 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-methoxybutyl]-, zinc salt (2:1) (9CI) (CA INDEX NAME)

Absolute stereochemistry.



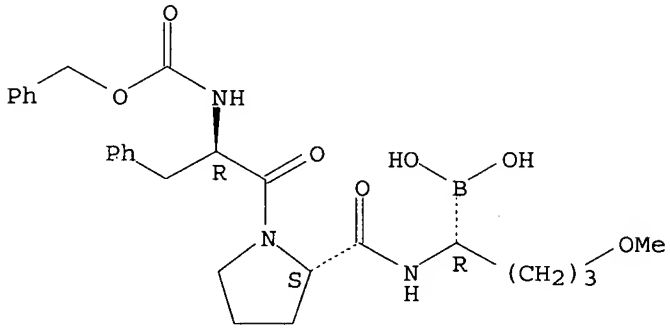
●1/2 Zn

RN 871576-04-4 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-methoxybutyl]-, compd. with L-arginine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 871576-03-3
CMF C27 H36 B N3 O7

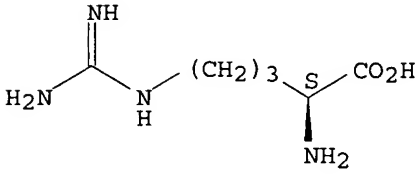
Absolute stereochemistry.



CM 2

CRN 74-79-3
CMF C6 H14 N4 O2

Absolute stereochemistry.

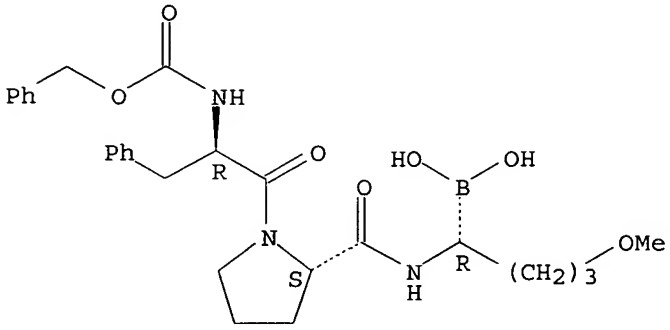


RN 871576-05-5 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-methoxybutyl]-, compd. with L-lysine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 871576-03-3
CMF C27 H36 B N3 O7

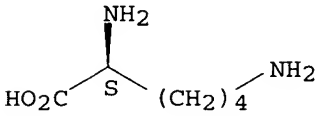
Absolute stereochemistry.



CM 2

CRN 56-87-1
CMF C6 H14 N2 O2

Absolute stereochemistry.

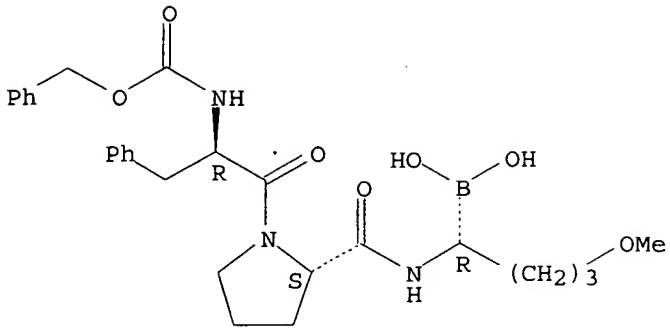


RN 871576-06-6 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-methoxybutyl]-, compd. with 1-deoxy-1-(methylamino)-D-glucitol (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 871576-03-3
CMF C27 H36 B N3 O7

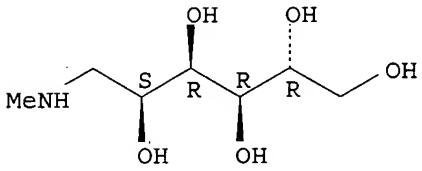
Absolute stereochemistry.



CM 2

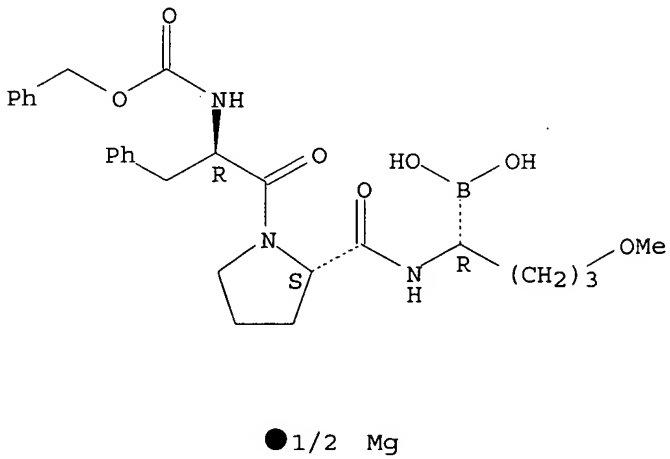
CRN 6284-40-8
CMF C7 H17 N O5

Absolute stereochemistry.



RN 871576-08-8 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-methoxybutyl]-, magnesium salt (2:1) (9CI) (CA INDEX NAME)

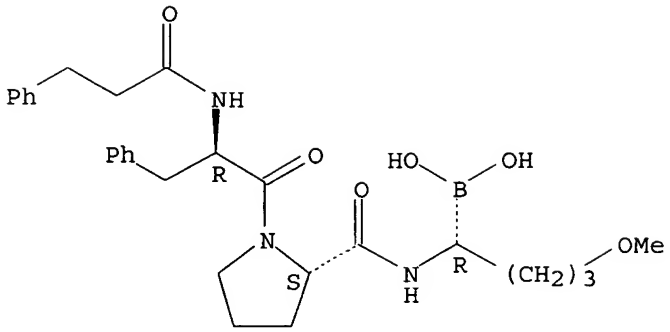
Absolute stereochemistry.



●1/2 Mg

RN 871576-12-4 HCAPLUS
CN L-Prolinamide, N-(1-oxo-3-phenylpropyl)-D-phenylalanyl-N-[(1R)-1-borono-4-methoxybutyl]-, monosodium salt (9CI) (CA INDEX NAME)

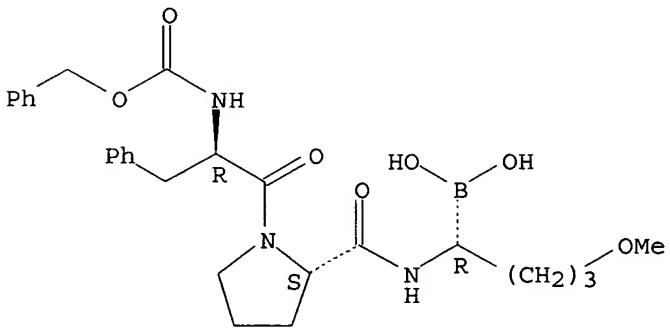
Absolute stereochemistry.



● Na

IT **871576-03-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptide boronic acids as anticoagulants)
RN 871576-03-3 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 2 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1033684 HCAPLUS
DOCUMENT NUMBER: 143:339335
TITLE: Direct thrombin inhibitors are not equally effective in vivo against arterial thrombosis
AUTHOR(S): McBane, Robert D.; Hassinger, Nancy L.; Mruk, Jozef S.; Grill, Diane E.; Chesebro, James H.
CORPORATE SOURCE: Division of Cardiovascular Medicine, Mayo Clinic and Foundation for Education and Research, Rochester, MN, 55905, USA
SOURCE: Thrombosis Research (2005), 116(6), 525-532
CODEN: THBRAA; ISSN: 0049-3848
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

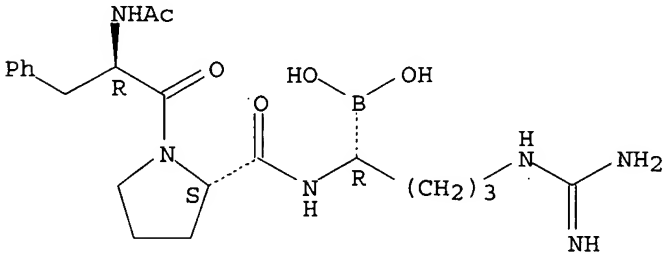
AB Background: Qual. differences in antithrombotic efficacy between thrombin inhibitors may be explained by the affinity for which they bind thrombin. This affinity is inversely proportional to the inhibitory constant for the agent (Ki). Thrombin inhibitors, DuP714 (Ki = 10- 11) and argatroban (Ki = 10- 8), were compared to our previous studies with r-hirudin (Ki = 10- 13). Methods and results: Prior to balloon angioplasty, thirty pigs randomly received DuP714 (0.1 mg/kg bolus and 0.6 mg/kg/h infusion; n = 8), argatroban (0.2 mg/kg/min. continuous infusion; n = 9), or saline (n = 17). Injured arterial segments were measured for 111In-platelet and 125I-fibrin(ogen) deposition and the incidence of macroscopic thrombus. In DuP714-treated animals, platelet and fibrin(ogen) deposition were significantly lower than controls in both carotid (10 ± 2 vs. 62 ± 18 and 20 ± 4 vs. 74 ± 6) and coronary (10 ± 4 vs. 160 ± 63 and 17 ± 3 vs. 86 ± 22) arteries ($p < 0.005$). In contrast, platelet and fibrin(ogen) deposition were similar when comparing argatroban to saline in carotid (41 ± 20 vs. 40 ± 9 and 71 ± 5 vs. 49 ± 7) and coronary (92 ± 33 vs. 151 ± 45 and 114 ± 37 vs. 89 ± 38) arteries ($p = 0.82$ and 0.38, resp.). Compared to argatroban, fibrin(ogen) ($p < 0.001$) and coronary platelet deposition ($p < 0.05$) were significantly reduced in animals treated with DuP714 with no significant difference in carotid platelet deposition ($p = 0.10$). Neither inhibitor prevented macroscopic thrombosis. In previous studies with r-hirudin in this model, platelet deposition was limited to a monolayer with complete inhibition of macroscopic thrombus. Conclusions: Direct thrombin inhibitors do not equally prevent arterial thrombosis. Qual. differences may be explained in part by the affinity for which they bind thrombin.

IT **130982-43-3**, DuP714
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(direct thrombin inhibitors are not equally effective in vivo against arterial thrombosis)

RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1004574 HCAPLUS
DOCUMENT NUMBER: 143:306408
TITLE: Preparation of boronate medicaments for preventing thrombosis during surgery
INVENTOR(S): Combe-Marzelle, Sophie Marie; Kakkar, Sanjay Kumar; Allen, Graham Douglas
PATENT ASSIGNEE(S): Trigen Limited, UK

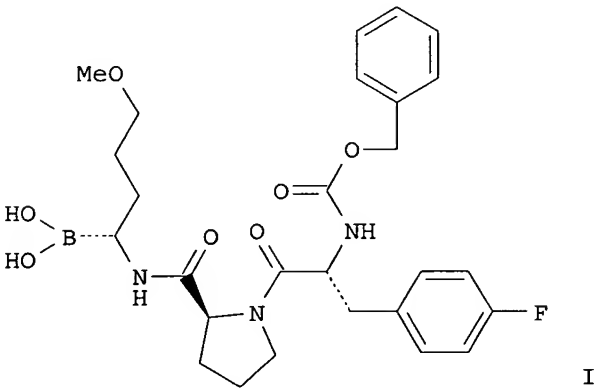
SOURCE: PCT Int. Appl., 107 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005084686	A2	20050915	WO 2005-GB908	20050309
WO 2005084686	A3	20051201		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2004-5280 A 20040309
OTHER SOURCE(S): MARPAT 143:306408
GI



I

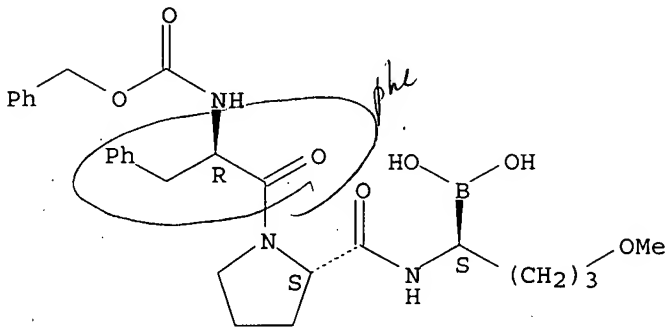
AB The use for the manufacture of a medicament for preventing unwanted coagulation during surgery, and particularly a Coronary Artery Bypass Graft (CABG) procedure, comprises boronic acids and salts, prodrugs and prodrug salts. E.g., I was prepared as well as salts such as Na, Ca and amino acid salts. Examples also were given for i.v. administration to humans and mitral valve repair.

IT **667917-16-0P**
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of boronate medicaments for preventing thrombosis during surgery)

RN 667917-16-0 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

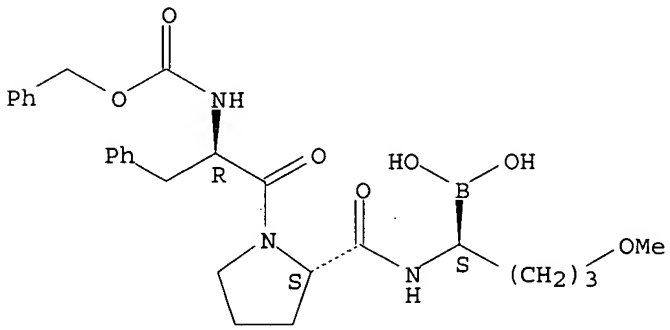


IT **667917-15-9P 667917-80-8P 667917-82-0P**
667917-83-1P 861229-95-0P 864547-26-2P
864547-27-3P 864547-29-5P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of boronate medicaments for preventing thrombosis during surgery)

RN 667917-15-9 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, calcium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

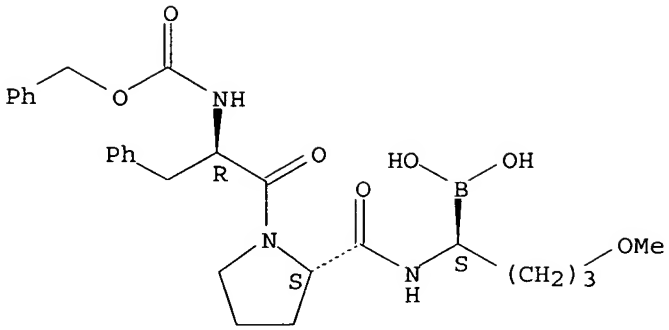


●x Ca

RN 667917-80-8 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, lithium salt (9CI) (CA INDEX NAME)

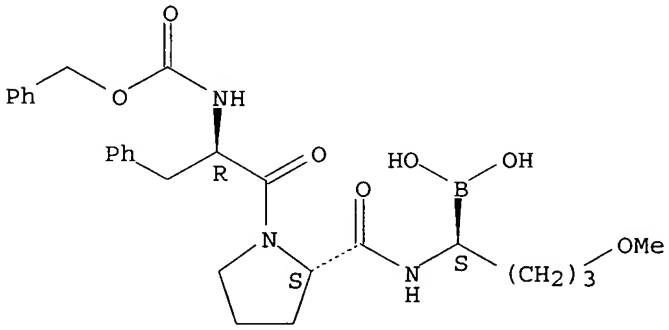
Absolute stereochemistry.



●x Li

RN 667917-82-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, sodium salt (9CI) (CA INDEX NAME)

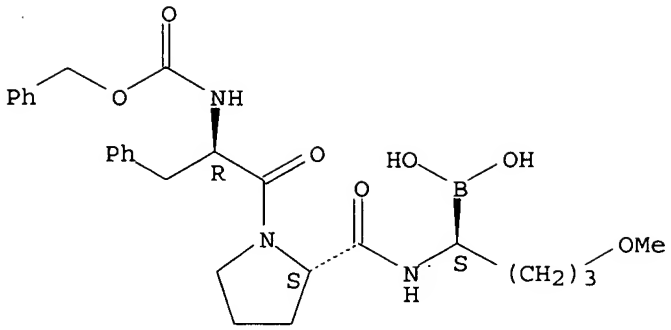
Absolute stereochemistry.



●x Na

RN 667917-83-1 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, potassium salt (9CI) (CA INDEX NAME)

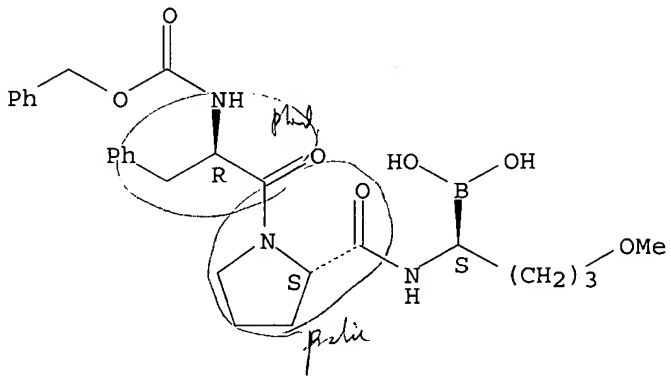
Absolute stereochemistry.



●x K

RN 861229-95-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, magnesium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



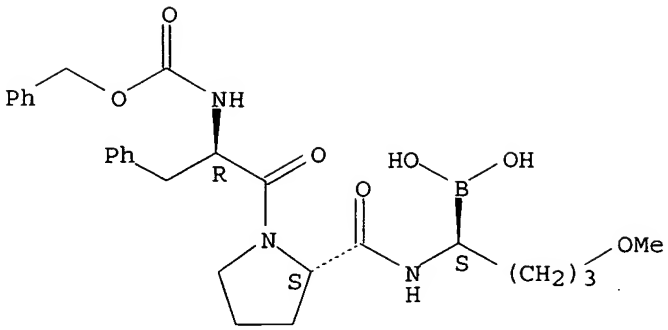
●x Mg

RN 864547-26-2 HCAPLUS
CN L-Arginine, compd. with N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-L-prolinamide (9CI) (CA INDEX NAME)

CM 1

CRN 667917-16-0
CMF C27 H36 B N3 O7

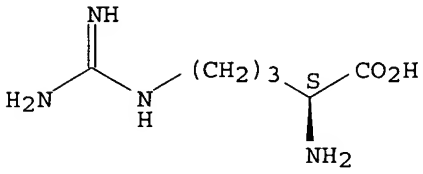
Absolute stereochemistry.



CM 2

CRN 74-79-3
CMF C6 H14 N4 O2

Absolute stereochemistry.

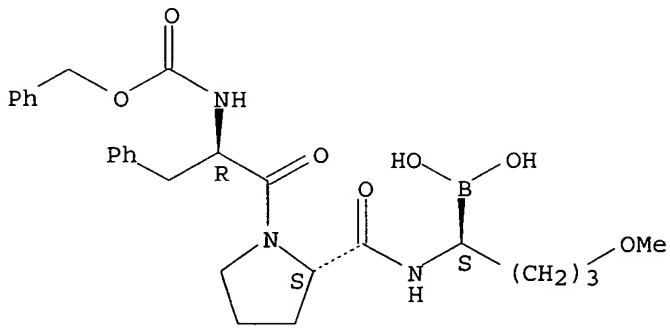


RN 864547-27-3 HCAPLUS
CN L-Lysine, compd. with N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-L-prolinamide (9CI) (CA INDEX NAME)

CM 1

CRN 667917-16-0
CMF C27 H36 B N3 O7

Absolute stereochemistry.

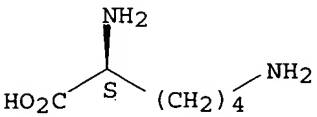


CM 2

CRN 56-87-1

CMF C6 H14 N2 O2

Absolute stereochemistry.

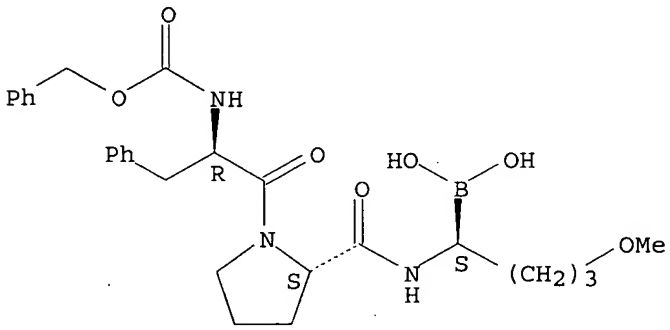


RN 864547-29-5 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, compd. with 1-deoxy-1-(methylamino)-D-glucitol (9CI) (CA INDEX NAME)

CM 1

CRN 667917-16-0
CMF C27 H36 B N3 O7

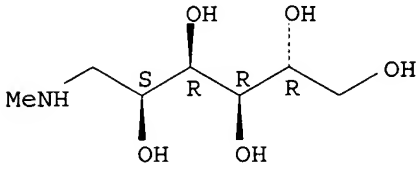
Absolute stereochemistry.



CM 2

CRN 6284-40-8
CMF C7 H17 N O5

Absolute stereochemistry.



L13 ANSWER 4 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1004573 HCAPLUS
DOCUMENT NUMBER: 143:311969
TITLE: Boronate medicaments suitable for short duration anticoagulation
INVENTOR(S): Patrick, Guy Michael; Combe-Marzelle, Sophie Marie;

Kennedy, Anthony James; Withington, Roger; Boucher, Oliver Vimpany Arnold
PATENT ASSIGNEE(S): Trigen Limited, UK
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005084685	A2	20050915	WO 2005-GB907	20050309
WO 2005084685	A3	20051124		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

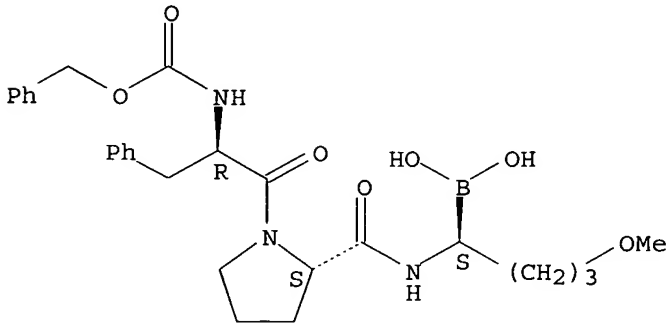
PRIORITY APPLN. INFO.: GB 2004-5272 A 20040309
OTHER SOURCE(S): MARPAT 143:311969

AB An oral dosage form of a compound selected from boronic acids which have a neutral thrombin (P1) domain linked to a hydrophobic moiety capable of binding to the thrombin (S2) and (S3) subsites, and salts, prodrugs and prodrug salts of such acids, the dosage form comprising a solid phase formulation comprising the compound and being adapted for reconstitution of the formulation to form a liquid preparation

IT **667917-16-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(boronate medicaments suitable for short duration anticoagulation)

RN 667917-16-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 5 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:735303 HCAPLUS
DOCUMENT NUMBER: 143:173146
TITLE: Preparation of peptide boronic acid salts for use in anti-thrombotic pharmaceutical formulations
INVENTOR(S): Madge, David Jonathan; Dolman, Mark; Walter, Armin; Krimmer, Dieter; Deadman, John Joseph; Olbrich, Alfred; Weiland-Waibel, Andrea M. t.
PATENT ASSIGNEE(S): Trigen Limited, UK
SOURCE: U.S. Pat. Appl. Publ., 65 pp., Cont.-in-part of U.S. Ser. No. 659,179.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005176651	A1	20050811	US 2004-937854	20040908
AU 2003263328	A1	20040329	AU 2003-263328	20030909
AU 2003263333	A1	20040329	AU 2003-263333	20030909
AU 2003263343	A1	20040329	AU 2003-263343	20030909
US 2004138175	A1	20040715	US 2003-658971	20030909
US 2004147453	A1	20040729	US 2003-659179	20030909
EP 1466916	A1	20041013	EP 2004-76510	20030909
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
EP 1466917	A1	20041013	EP 2004-76521	20030909
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003014450	A	20050726	BR 2003-14450	20030909
BR 2003014518	A	20050726	BR 2003-14518	20030909
EP 1561466	A2	20050810	EP 2004-76548	20030909
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005288253	A1	20051229	US 2003-659178	20030909
JP 2006503903	T2	20060202	JP 2004-569794	20030909
US 2005282757	A1	20051222	US 2005-78097	20050309

PRIORITY APPLN. INFO.:

GB 2002-20764	A	20020909
GB 2002-20822	A	20020909
GB 2003-7817	A	20030404
GB 2003-11237	A	20030516
GB 2003-15691	A	20030704
US 2003-501718P	P	20030909
US 2003-658971	A2	20030909
US 2003-659178	A2	20030909
US 2003-659179	A2	20030909
US 2003-485786P	P	20030708
EP 2003-255590	A3	20030909
WO 2003-GB3883	W	20030909
WO 2003-GB3887	W	20030909
WO 2003-GB3897	W	20030909
US 2004-937181	A2	20040908
US 2004-937854	A2	20040908

OTHER SOURCE(S): MARPAT 143:173146

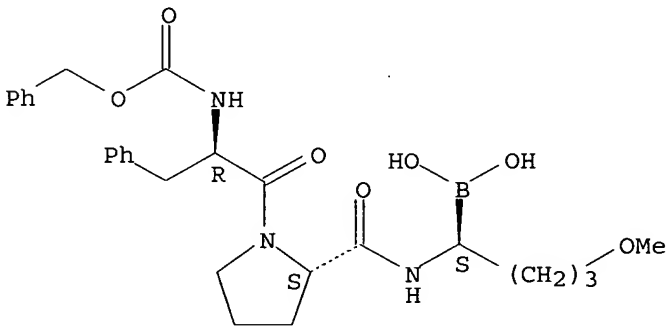
AB The invention relates to tripeptide boronic acids of (R,S,R) configuration, e.g., Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)2 (TRI 50c; Mpg = 3-methoxypropylglycine residue; Cbz = benzyloxycarbonyl), and their use to make base addition salts which are formulated into anti-thrombotic

pharmaceutical formulations. Thus, TRI 50c pinacol ester and magnesium salt were prepared and their activities in a thrombin amidolytic assay shown in a figure. TRI 50c and novel products of the invention are effective in arterial as well as venous contexts.

IT **667917-15-9P 667917-16-0DP**, complexes with zinc
667917-16-0P 667917-80-8P 667917-82-0P
667917-83-1P 667917-86-4P 667917-88-6P
861229-94-9P 861229-95-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide boronic acid salts for use in anti-thrombotic pharmaceutical formulations)

RN 667917-15-9 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, calcium salt (9CI) (CA INDEX NAME)

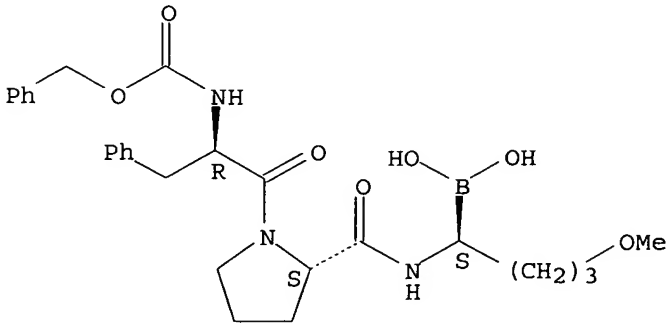
Absolute stereochemistry.



●x Ca

RN 667917-16-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

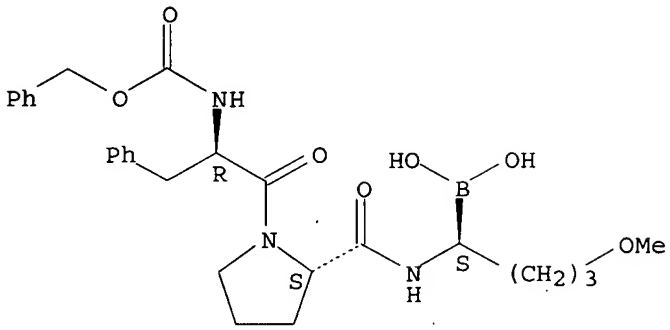
Absolute stereochemistry.



RN 667917-16-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-

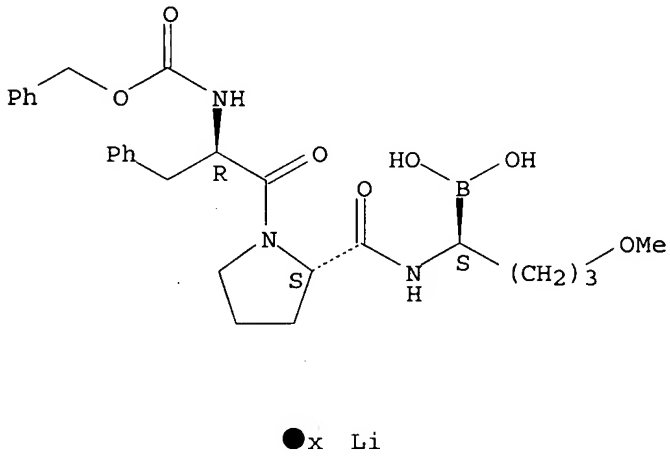
4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 667917-80-8 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, lithium salt (9CI) (CA INDEX NAME)

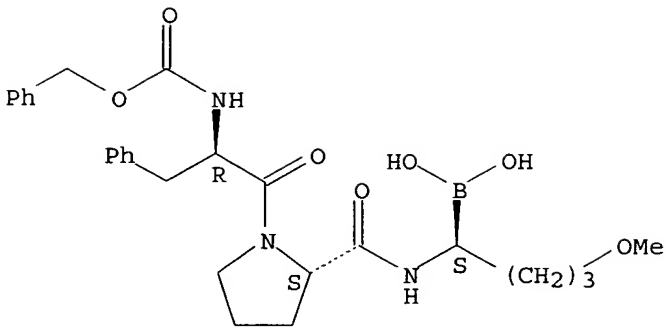
Absolute stereochemistry.



●x Li

RN 667917-82-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, sodium salt (9CI) (CA INDEX NAME)

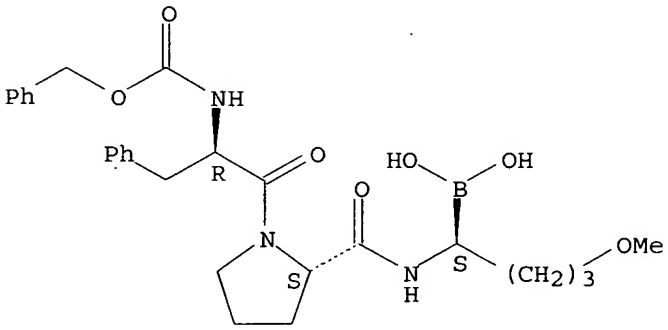
Absolute stereochemistry.



●x Na

RN 667917-83-1 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, potassium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



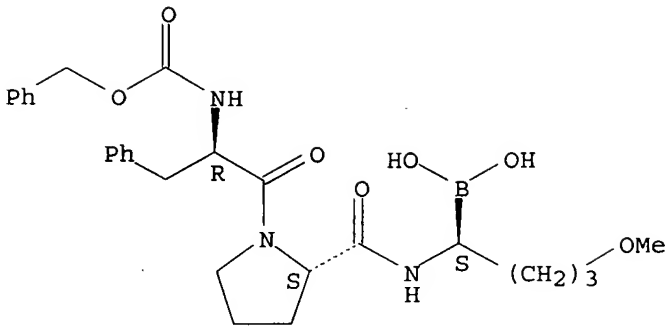
●x K

RN 667917-86-4 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, compd. with L-arginine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 667917-16-0
CMF C27 H36 B N3 O7

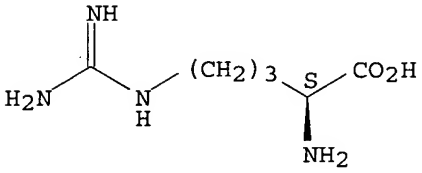
Absolute stereochemistry.



CM 2

CRN 74-79-3
CMF C6 H14 N4 O2

Absolute stereochemistry.

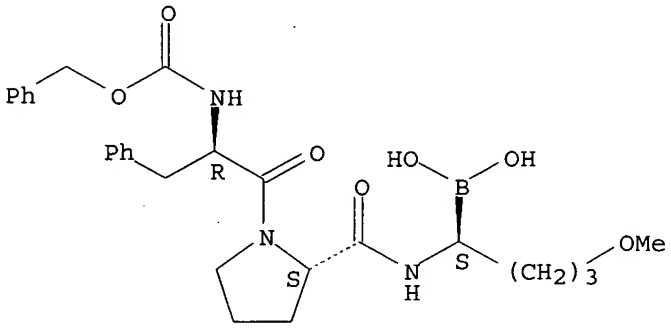


RN 667917-88-6 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, compd. with L-lysine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 667917-16-0
CMF C27 H36 B N3 O7

Absolute stereochemistry.

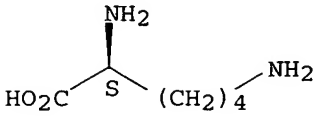


CM 2

CRN 56-87-1

CMF C6 H14 N2 O2

Absolute stereochemistry.

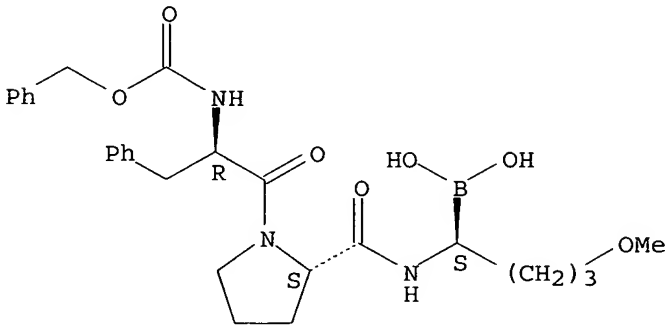


RN 861229-94-9 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, compd. with 1-deoxy-1-(methylamino)-D-glucitol (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 667917-16-0
CMF C27 H36 B N3 O7

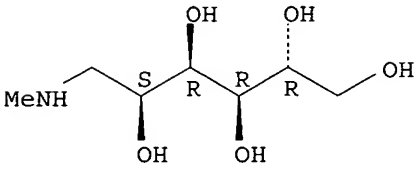
Absolute stereochemistry.



CM 2

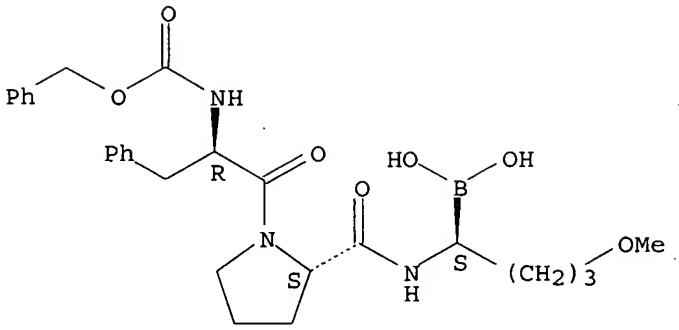
CRN 6284-40-8
CMF C7 H17 N O5

Absolute stereochemistry.



RN 861229-95-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, magnesium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●x Mg

L13 ANSWER 6 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:474929 HCAPLUS
DOCUMENT NUMBER: 143:7986
TITLE: Method for synthesizing peptide boronic acids
INVENTOR(S): Walter, Armin; Olbrich, Alfred; Weiland-Waibel, Andrea M. T.; Krimmer, Dieter
PATENT ASSIGNEE(S): Trigen Limited, Switz.
SOURCE: U.S. Pat. Appl. Publ., 43 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

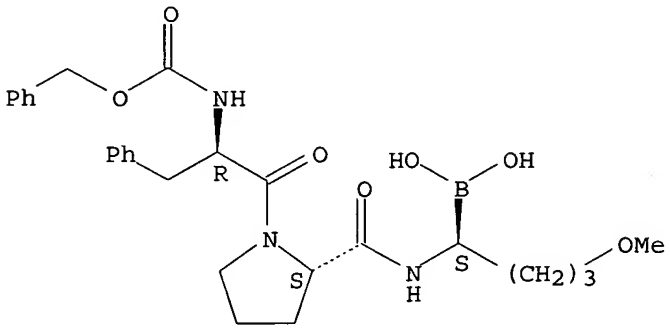
PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005119226	A1	20050602	US 2004-937181		20040908
US 2005282757	A1	20051222	US 2005-78097		20050309
PRIORITY APPLN. INFO.:			US 2003-501718P	P	20030909
			GB 2002-20764	A	20020909
			GB 2002-20822	A	20020909
			GB 2003-7817	A	20030404
			GB 2003-11237	A	20030516
			GB 2003-15691	A	20030704
			US 2003-658971	A2	20030909
			US 2003-659178	A2	20030909
			US 2003-659179	A2	20030909
			US 2004-937181	A2	20040908
			US 2004-937854	A2	20040908

OTHER SOURCE(S): MARPAT 143:7986
AB Organoboronic acids, e.g., Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)2 (Mpg = 3-methoxypropylglycine residue; Cbz = benzyloxycarbonyl), are made by hydrolyzing their diethanolamine adducts under conditions which avoid substantial C-B bond breakage. The product acids are substantially free of degradation product derived from cleavage of the C-B bond and are converted into base addition salts for use in anti-thrombotic pharmaceutical formulations.
IT **667917-15-9P 667917-16-0P 667917-82-0P**
852457-84-2P
RL: SPN (Synthetic preparation); PREP (Preparation)

(synthesis of peptide boronic acids via cleavage of diethanolamine adducts)

RN 667917-15-9 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, calcium salt (9CI) (CA INDEX NAME)

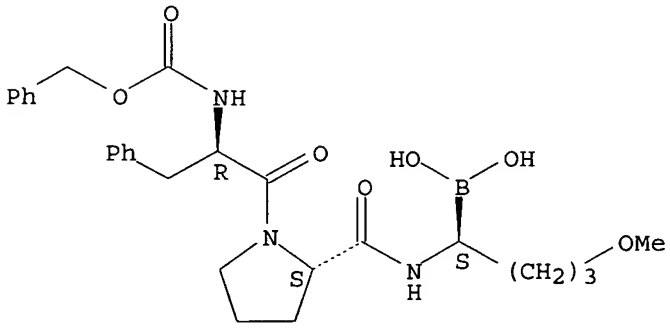
Absolute stereochemistry.



●x Ca

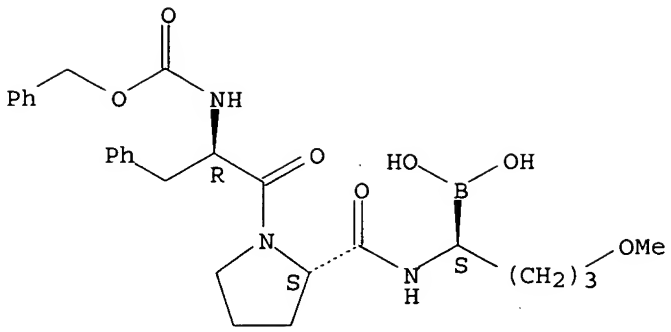
RN 667917-16-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 667917-82-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, sodium salt (9CI) (CA INDEX NAME)

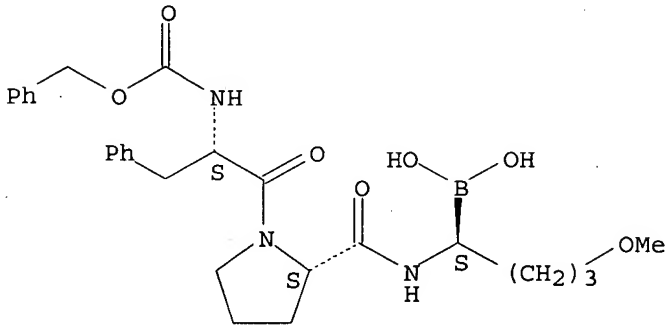
Absolute stereochemistry.



●x Na

RN 852457-84-2 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-L-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 7 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:198296 HCAPLUS
DOCUMENT NUMBER: 140:229444
TITLE: Boronic acid salts and use thereof in the preparation of medicaments for treating thrombosis
INVENTOR(S): Madge, David Jonathan; Dolman, Mark; Combe-Marzelle, Sophie Marie; Deadman, John Joseph; Kennedy, Anthony James; Kakkar, Sanjay Kumar
PATENT ASSIGNEE(S): Trigen Limited, UK
SOURCE: Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1396270	A1	20040310	EP 2003-255629	20030909
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WO 2004022070 A1 20040318 WO 2003-GB3883 20030909
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WO 2004022071 A1 20040318 WO 2003-GB3887 20030909
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WO 2004022072 A1 20040318 WO 2003-GB3897 20030909
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EP 1400245 A1 20040324 EP 2003-255590 20030909
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AU 2003263328 A1 20040329 AU 2003-263328 20030909
AU 2003263333 A1 20040329 AU 2003-263333 20030909
AU 2003263343 A1 20040329 AU 2003-263343 20030909
EP 1466916 A1 20041013 EP 2004-76510 20030909
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EP 1466917 A1 20041013 EP 2004-76521 20030909
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BR 2003014450 A 20050726 BR 2003-14450 20030909
BR 2003014518 A 20050726 BR 2003-14518 20030909
EP 1561466 A2 20050810 EP 2004-76548 20030909
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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JP 2006503903 T2 20060202 JP 2004-569794 20030909
PRIORITY APPLN. INFO.: GB 2002-20764 A 20020909
GB 2002-20822 A 20020909
GB 2003-7817 A 20030404
GB 2003-11237 A 20030516
GB 2003-15691 A 20030704
US 2003-485786P P 20030708
EP 2003-255590 A3 20030909

WO 2003-GB3883 W 20030909
WO 2003-GB3887 W 20030909
WO 2003-GB3897 W 20030909

OTHER SOURCE(S): MARPAT 140:229444

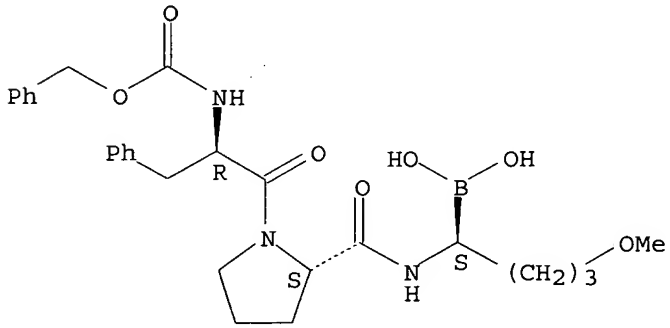
AB Salts of a peptide boronic acid drug, for example of Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)2 are described. The counter-ion to the boronate may be an alkali metal or derived from an organic nitrogen-containing compound The salts are used for the manufacture of a medicament for treating thrombosis.

IT **667917-16-0P**, TRI 50c
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation, antithrombotic activity, bioavailability and properties of oral boronic acid salts)

RN 667917-16-0 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

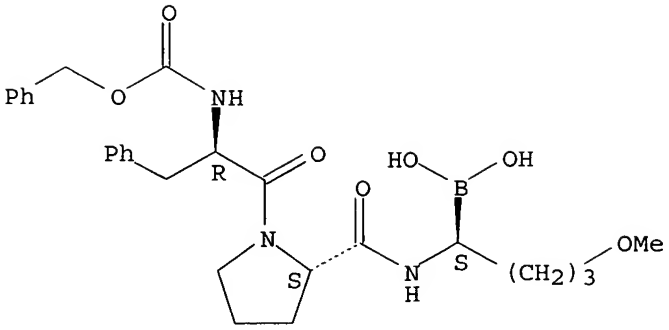


IT **667917-16-0DP**, complexes with tri 50c **667917-80-8P** **667917-82-0P** **667917-83-1P** **667917-86-4P** **667917-88-6P** **667917-90-0P**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation, antithrombotic activity, bioavailability and properties of oral boronic acid salts)

RN 667917-16-0 HCAPLUS

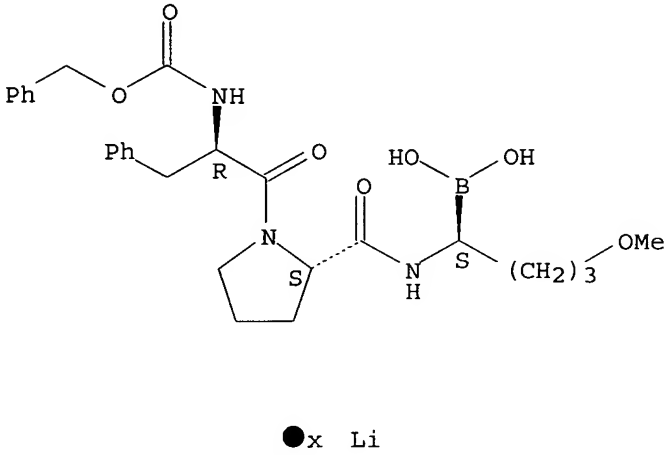
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 667917-80-8 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, lithium salt (9CI) (CA INDEX NAME)

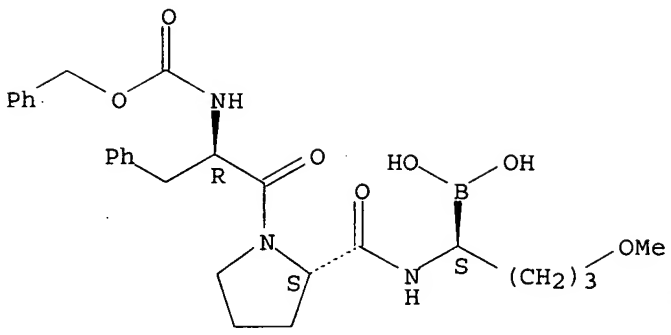
Absolute stereochemistry.



●x Li

RN 667917-82-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, sodium salt (9CI) (CA INDEX NAME)

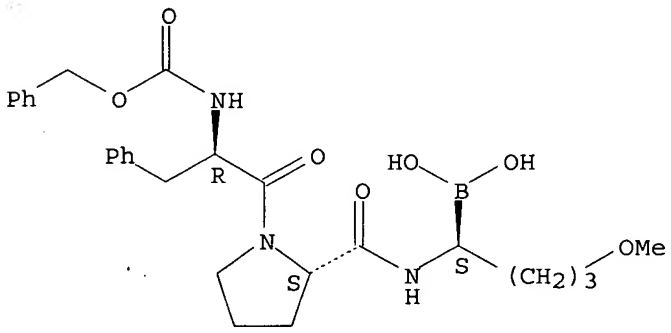
Absolute stereochemistry.



●x Na

RN 667917-83-1 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, potassium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



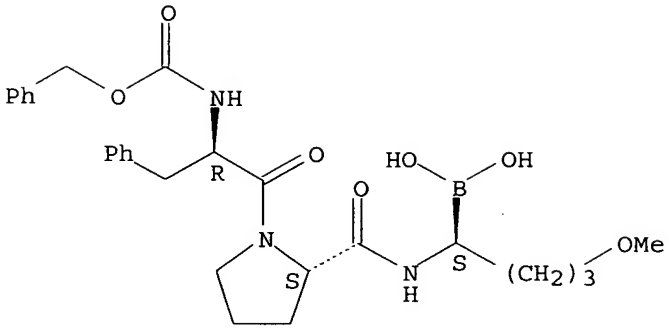
●x K

RN 667917-86-4 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, compd. with L-arginine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 667917-16-0
CMF C27 H36 B N3 O7

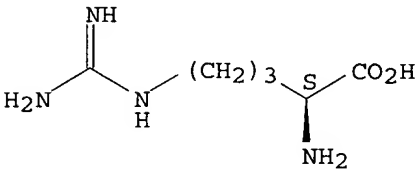
Absolute stereochemistry.



CM 2

CRN 74-79-3
CMF C6 H14 N4 O2

Absolute stereochemistry.

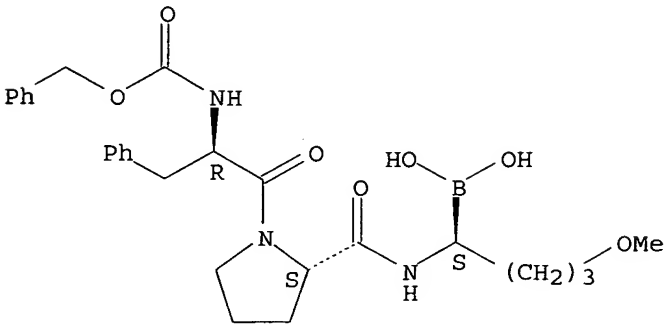


RN 667917-88-6 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, compd. with L-lysine (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 667917-16-0
CMF C27 H36 B N3 O7

Absolute stereochemistry.

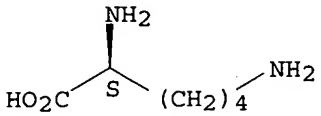


CM 2

CRN 56-87-1

CMF C6 H14 N2 O2

Absolute stereochemistry.

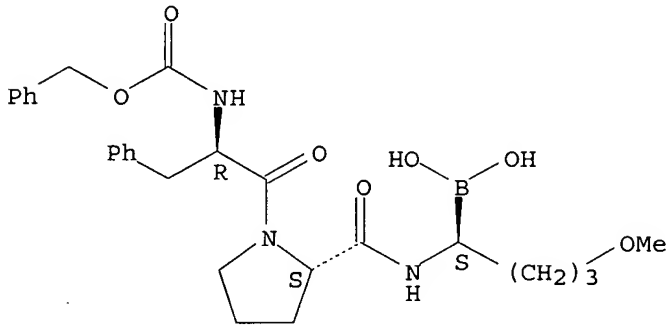


RN 667917-90-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, compd. with 2-deoxy-2-(methylamino)-D-glucose (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 667917-16-0
CMF C27 H36 B N3 O7

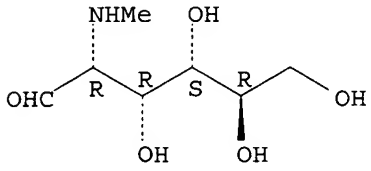
Absolute stereochemistry.



CM 2

CRN 3329-30-4
CMF C7 H15 N O5

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 8 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:198295 HCAPLUS
DOCUMENT NUMBER: 140:229443
TITLE: Boronic acid salts of multivalent metals used in the

preparation of a medicament for treating thrombosis

INVENTOR(S): Madge, David Jonathan; Dolman, Mark; Combe-Marzelle, Sophie Marie; Deadman, John Joseph; Kennedy, Antony James; Kakkar, Sanjay Kumar; Chahwala, Suresh Babubhai; Boucher, Oliver Vimpany Arnold; Walter, Armin; Olbrich, Alfred; Krimmer, Dieter; Weiland-Weibel, Andrea Maria Theresia

PATENT ASSIGNEE(S): Trigen Limited, UK

SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1396269	A1	20040310	EP 2003-255604	20030909
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EP 1400245	A1	20040324	EP 2003-255590	20030909
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AU 2003263333	A1	20040329	AU 2003-263333	20030909
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EP 1466916	A1	20041013	EP 2004-76510		20030909
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EP 1466917	A1	20041013	EP 2004-76521		20030909
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003014450	A	20050726	BR 2003-14450		20030909
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EP 1561466	A2	20050810	EP 2004-76548		20030909
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JP 2006503903	T2	20060202	JP 2004-569794		20030909
PRIORITY APPLN. INFO.:			GB 2002-20764	A	20020909
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			GB 2003-15691	A	20030704
			US 2003-485786P	P	20030708
			EP 2003-255590	A3	20030909
			WO 2003-GB3883	W	20030909
			WO 2003-GB3887	W	20030909
			WO 2003-GB3897	W	20030909

OTHER SOURCE(S): MARPAT 140:229443

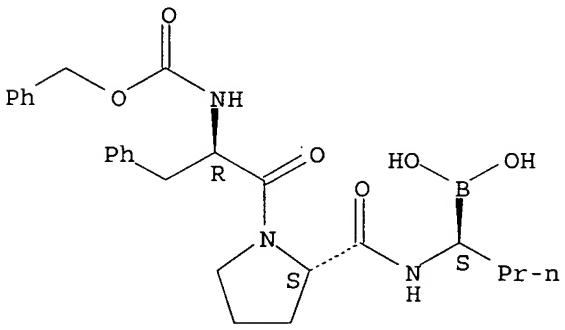
AB Salts of a pharmaceutically acceptable divalent metal and an organoboronic acid as selective thrombin inhibitors are described. Examples of such metals are calcium, magnesium and zinc. The organoboronic acid drug may be a boropeptide protease inhibitor. The salts may be formulated in oral dosage form, such as a capsule or compressed tablet.

IT **667917-17-1**
RL: MSC (Miscellaneous)
(impurity; preparation of antithrombotic boronic acid salts of multivalent metals free of impurities)

RN 667917-17-1 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-boronobutyl]- (9CI) (CA INDEX NAME)

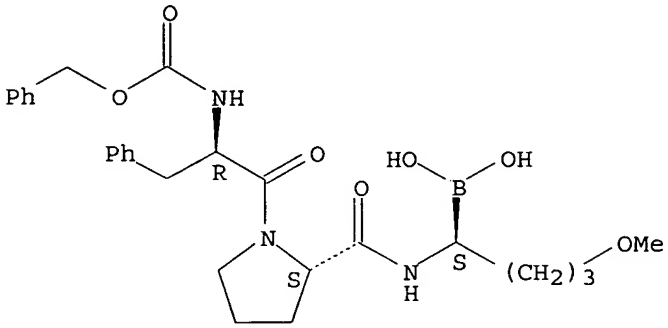
Absolute stereochemistry.



IT **667917-16-0P**, TRI 50C
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation, antithrombotic activity, bioavailability and properties of oral boronic acid salts of multivalent metals)

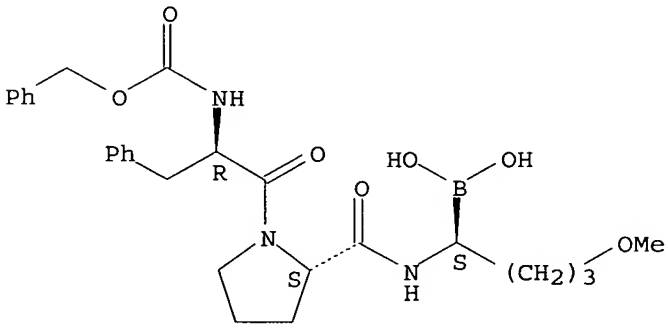
RN 667917-16-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **667917-15-9P 667917-16-0DP**, Complexes with zinc or magnesium
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation, antithrombotic activity, bioavailability and properties of oral boronic acid salts of multivalent metals)
RN 667917-15-9 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, calcium salt (9CI) (CA INDEX NAME)

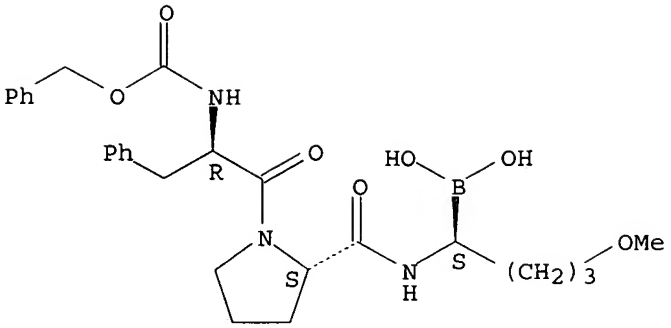
Absolute stereochemistry.



●x Ca

RN 667917-16-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

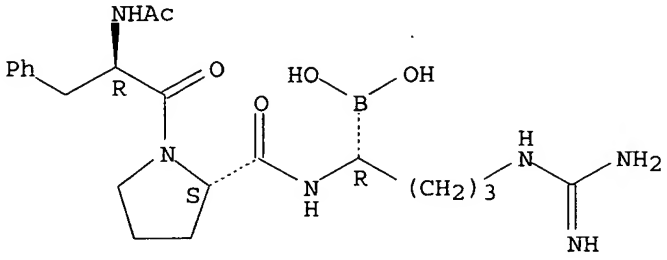
L13 ANSWER 9 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:261187 HCAPLUS
DOCUMENT NUMBER: 133:205008
TITLE: Evaluation of Argatroban and DUP 714 as anticoagulants for blood gas, electrolyte and ionized calcium analyses
AUTHOR(S): Lyon, M. E.; Harding, S. Rutledge; Oosman, S. N.; Lyon, A. W.
CORPORATE SOURCE: Department of Pharmacology, University of Saskatchewan, Saskatoon, SK, S7N 5E5, Can.
SOURCE: Scandinavian Journal of Clinical and Laboratory Investigation (2000), 60(1), 19-25
CODEN: SJCLAY; ISSN: 0036-5513
PUBLISHER: Taylor & Francis AS
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective of this study was to determine if the thrombin inhibitors Argatroban and DUP 714 could anticoagulate whole blood without influencing the analyses of blood gases, electrolytes, ionized calcium or CO-oximetry. The anticoagulant potency of DUP 714 (0.5-68 μmol/l) and Argatroban (1.5-390 μmol/l) was evaluated using the activated partial thromboplastin time (APTT), prothrombin time (PT) and whole blood clot time (WBCT). APTT and the PT were measured using a Behring Fibrintimer. APTT was found to be more sensitive to prolongation by both of the thrombin inhibitors than were the PT or WBCT assays. DUP 714 was found to a more potent anticoagulant than Argatroban. DUP 714 anticoagulated specimens (>2.2 μmol/l) did not clot for at least 2 days, whereas Argatroban preserved specimens (390 μmol/l) clotted within 5.5 h of collection. No statistically significant changes in the measurement of pH, PCO2, PO2, Na, K, ionized calcium, oxyHb, deoxyHb, metHb or carboxyHb (measured using a Corning 288 Blood Gas/Electrolyte Analyzer and a Corning 270 CO-oximeter) were detected in DUP 714 (34 μmol/l) or Argatroban (390 μmol/l) anticoagulated whole blood specimens. In conclusion, DUP 714 and Argatroban are suitable anticoagulants for preserving blood prior to blood gas and electrolyte analyses.

IT **130982-43-3**, DuP 714
RL: ARU (Analytical role, unclassified); BUU (Biological use, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(evaluation of Argatroban and DUP 714 as anticoagulants for blood gas, electrolyte and ionized calcium analyses)
RN 130982-43-3 HCAPLUS

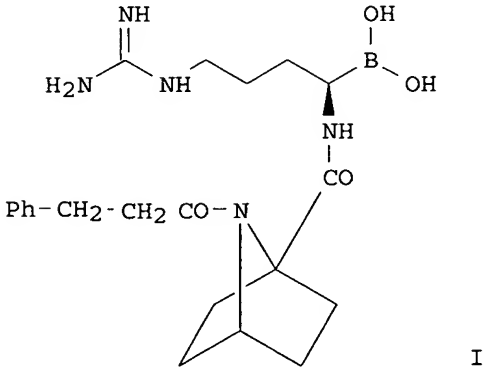
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 10 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:758007 HCAPLUS
DOCUMENT NUMBER: 132:108287
TITLE: 7-Azabicycloheptane Carboxylic Acid: A Proline Replacement in a Boroarginine Thrombin Inhibitor
AUTHOR(S): Han, Wei; Pelletier, Jeffrey C.; Mersinger, Lawrence J.; Kettner, Charles A.; Hodge, C. Nicholas
CORPORATE SOURCE: Department of Chemical and Physical Sciences, DuPont Pharmaceuticals Company, Wilmington, DE, 19880, USA
SOURCE: Organic Letters (1999), 1(12), 1875-1877
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

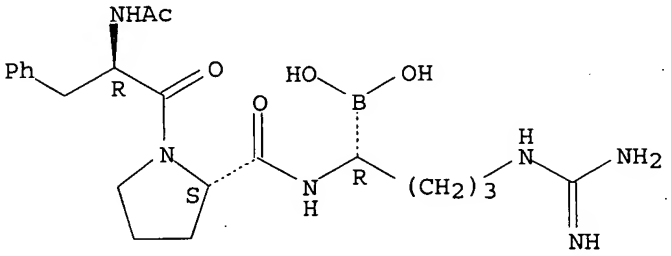
AB The synthesis of thrombin inhibitor (I), which incorporates conformationally constrained 7-azabicycloheptane carboxylic acid (II) as a proline replacement, is described. The inhibition constant (Ki(thrombin) = 2.9 nM) indicates that II is a reasonable replacement of proline in the formation of a β-turn tripeptide mimetic.

IT **130982-43-3**, Dup 714
RL: MSC (Miscellaneous)

(7-azabicycloheptane carboxylic acid-containing boroarginine peptidomimetic of as thrombin inhibitor)

RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

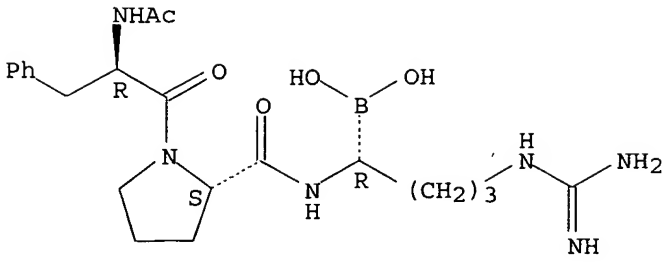
L13 ANSWER 11 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:725330 HCAPLUS
DOCUMENT NUMBER: 132:44457
TITLE: Improvement of the intestinal absorption of a peptidomimetic, boronic acid thrombin inhibitor possibly utilizing the oligopeptide transporter
AUTHOR(S): Saitoh, Hiroshi; Aungst, Bruce J.
CORPORATE SOURCE: DuPont Pharmaceuticals Research Laboratories, Wilmington, DE, 19880-0400, USA
SOURCE: Pharmaceutical Research (1999), 16(11), 1786-1789
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors evaluated the in vitro rat jejunal permeability of DuP 714 and several m-cyano-substituted borophenylalanine analogs. The authors investigated the effects of replacing the strongly basic boroarginine group and of N-terminal α-amino modifications on intestinal permeation. The results show that DuP 714 and three of the four m-cyano-substituted borophenylalanine analogs have rat intestinal permeability at least as poor as that of cefazolin. One analog having a free α-amino group had relatively good absorptive permeation, and its permeation was inhibited by known substrates of the oligopeptide transporter. These results imply that high intestinal permeation of this analog is at least partly mediated by the oligopeptide transport system.

IT **130982-43-3**, DuP 714 **197913-52-3**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(improvement of intestinal absorption of a peptidomimetic boronic acid thrombin inhibitor possibly utilizing oligopeptide transporter)

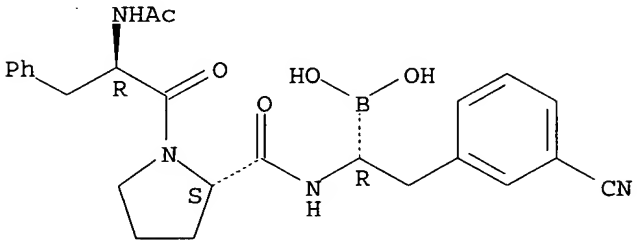
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 197913-52-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-1-borono-2-(3-cyanophenyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

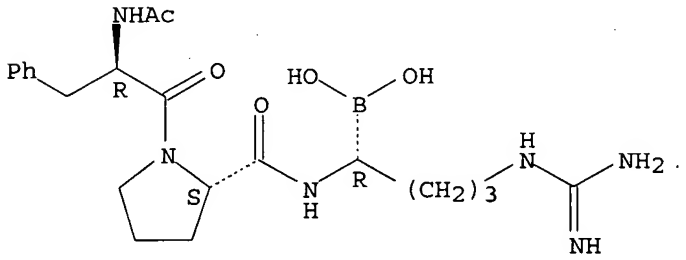
L13 ANSWER 12 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:163666 HCAPLUS
DOCUMENT NUMBER: 130:282342
TITLE: Positive-Ion Analysis of Boropeptides by Chemical Ionization and Liquid Secondary Ionization Mass Spectrometry
AUTHOR(S): Haas, Michael J.; Blom, Karl F.; Schwarz, Carl H., III
CORPORATE SOURCE: DuPont Pharmaceuticals Co., Wilmington, DE, 19880-0500, USA
SOURCE: Analytical Chemistry (1999), 71(8), 1574-1578
CODEN: ANCHAM; ISSN: 0003-2700
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Techniques for the characterization of two boronic acid peptides as their cyclic boronate ester derivs. by pos.-ion ammonia chemical ionization (CI) and pos.-ion liquid secondary ionization (LSIMS) are described and results presented. These techniques avoid the complications introduced by the thermally induced processes that boronic acids may undergo when the mass spectrometric characterizations of free boronic acids are attempted. Derivatizations for CI anal. were accomplished via a simple benchtop method using several polyfunctional nucleophilic derivatizing agents (ethylene glycol, glycerol, et al.), while derivatizations for LSIMS anal. were accomplished via both benchtop and previously established in situ methods using the same derivatizing agents. Certain previously held misconceptions about the LSIMS mass spectrometry of boronic acids are examined
IT **131062-98-1**

RL: ANT (Analyte); ANST (Analytical study)
(pos.-ion anal. of boropeptides by chemical ionization and liquid secondary ionization mass spectrometry)

RN 131062-98-1 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 13 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:662227 HCAPLUS

DOCUMENT NUMBER: 129:270386

TITLE: Thrombin and human plasma kallikrein inhibition during simulated extracorporeal circulation block platelet and neutrophil activation

AUTHOR(S): Wachtvogel, Yanina T.; Kettner, Charles; Hack, C. Erik; Huijens, Jan H.; Reilly, Thomas M.; Knabb, Robert M.; Kucich, Umberto; Niewiarowski, Stefan; Edmunds, L. Henry, Jr.; Colman, Robert W.

CORPORATE SOURCE: Sol Sherry Thrombosis Research Center, Dep. Medicine, School Medicine, Temple Univ., Philadelphia, PA, USA

SOURCE: Thrombosis and Haemostasis (1998), 80(4), 686-691
CODEN: THHADQ; ISSN: 0340-6245

PUBLISHER: F. K. Schattauer Verlagsgesellschaft mbH

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Cardiopulmonary bypass causes hemorrhagic complications, and initiates a chemical and cellular inflammatory response. Contact of blood with synthetic surfaces leads to qual. and quant. alterations in platelets, neutrophils, complement, and contact systems. Despite the fact that cardiopulmonary bypass is carried out in the presence of high doses of heparin, there is activation of both platelets and neutrophils. Thrombin is protected on cell and fibrin surfaces from antithrombin, even in the presence of high doses of heparin (5 U/mL). The authors studied the effect of a small (Mr = 497), highly effective (Ki = 41 pM), reversible tripeptide inhibitor of thrombin, DUP 714 (1 μM), in a well characterized model of simulated extracorporeal circulation. In the absence of DUP 714, platelet counts decreased by 75% 5 min after the start of extra-corporeal bypass and increased to 48% at 120 min of recirculation. DUP 714 preserved platelet counts, decreased plasma levels of platelet β-thromboglobulin levels, but did not prevent a decrease in sensitivity of platelets to ADP.

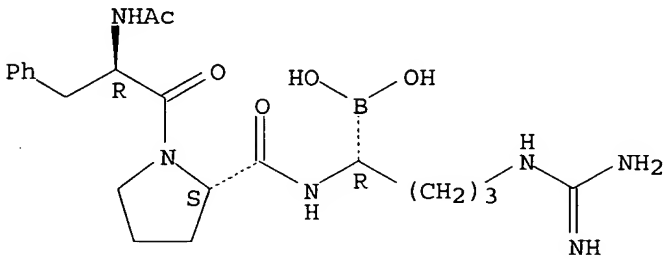
Kallikrein-C1-inhibitor and C1-C1-inhibitor complexes increased progressively from 0.32 U/mL to 0.67 U/mL and from 4.45 U/mL to 7.25 U/mL, resp., during 120 min of recirculation without DUP 714. Addition of DUP 714 inhibited kallikrein-C1-inhibitor complex formation but did not affect C1-C1-inhibitor complexes. In the absence of DUP 714, neutrophil elastase levels rose from a baseline of 0.01 to 1.18 μg/mL during 120 min of recirculation. Neutrophil elastase release at 120 min was inhibited in the presence of DUP 714 to 37% of the value with heparin alone. These results indicated that addition of this novel thrombin (and kallikrein) inhibitor to heparin preserved platelet counts, decreased platelet secretion, and provided the addnl. benefit of partially blocking neutrophil activation during simulated extra-corporeal circulation.

IT **130982-43-3**, DUP 714
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DUP 714 effect on thrombin and plasma kallikrein during extracorporeal circulation)

RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 14 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:605764 HCAPLUS

DOCUMENT NUMBER: 129:341097

TITLE: Bifunctional Peptide Boronate Inhibitors of Thrombin: Crystallographic Analysis of Inhibition Enhanced by Linkage to an Exosite 1 Binding Peptide

AUTHOR(S): Skordalakes, Emmanuel; Elgendy, Said; Goodwin, Christopher A.; Green, Donovan; Scully, Michael F.; Kakkar, Vijay V.; Freyssinet, Jean-Marie; Dodson, Guy; Deadman, John J.

CORPORATE SOURCE: Peptide Synthesis Section and Biochemistry Section, Thrombosis Research Institute, London, SW3 6LR, UK

SOURCE: Biochemistry (1998), 37(41), 14420-14427
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

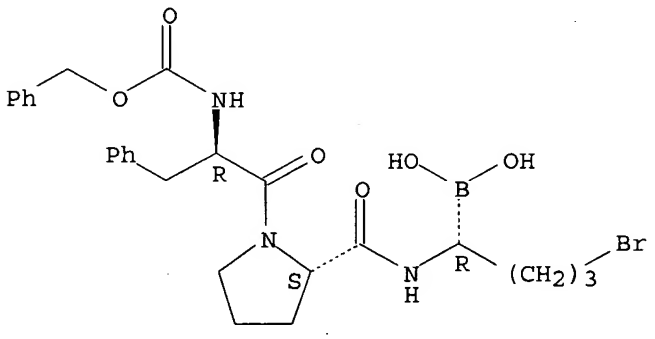
AB The affinity of the hirudin49-64 segment for exosite 1 of thrombin has been used previously to enhance the potency of simple competitive inhibitors [DiMaio, J., Gibbs, B., Munn, D., Lefebvre, J., Ni, F., Konishi, Y. (1990) J. Biol. Chemical 265, 21698-21703, and Maraganore, J. M., Bourdon, P., Jablonski, J., Ramachandran, K. L., and Fenton, J. W., II (1990) Biochem. 29, 7095-7087]. Using a similar approach, we have

enhanced the activity of two active site directed thrombin inhibitors by attaching this segment via a novel reverse oriented linker to each of two tripeptide boronate inhibitors. At P1, compound 1 contains an arginine-like, isothiouronium, side chain, while compound 2 contains an uncharged, bromopropyl residue. Inhibition of human α-thrombin by compound 1 shows slow, tight-binding competitive kinetics (final Ki of 2.2 pM, k1 of 3.51+107 M-1 s-1, and k-1 of 1.81+10-4 s-1). The addition of hirugen peptide (20 μM) competes for exosite 1 binding and restores the k1 and k-1 to that of the analogous tripeptide, 0.29+107 M-1 s-1 and 0.13+10-4 s-1, resp. Compound 1 has enhanced specificity for thrombin over trypsin with KiTry/KiThr of .apprx.900 compared to the analogous tripeptide, with KiTry/KiThr of .apprx.4. Compound 2 acts as a competitive inhibitor (KiThr of 0.6 nM) and is highly selective with no effect on trypsin. Crystallog. anal. of complexes of human α-thrombin with compound 1 (1.8 Å) and compound 2 (1.85 Å) shows a covalent bond between the boron of the inhibitor and Ser195 (bond lengths B-O of 1.55 and 1.61 Å, resp.). The isothiouronium group of compound 1 forms bidentate interactions with Asp189. The P2 and P3 residues of the inhibitors form interactions with the S2 and S3 sites of thrombin similar to other D-Phe-Pro based inhibitors [Bode, W., Turk, D., and Karshikov, A. (1992) Protein Sci. 1, 426-471.]. The linker exits the active site cleft of thrombin forming no interactions, while the binding of Hir49-64 segment to exosite 1 is similar to that previously described for hirudin [Rydel, T. J., Tulinsky, A., and Bode, W. (1991) J. Mol. Biol. 221, 583-601.]. Because of the similarity of binding at each of these sites to that of the analogous peptides added alone, this approach may be used to improve the inhibitory activity of all types of active site directed thrombin inhibitors and may also be applicable to the design of inhibitors of other proteases.

IT **143718-39-2 176701-90-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bifunctional peptide boronate inhibitors of thrombin, crystallog. anal. of inhibition enhanced by linkage to exosite 1 binding peptide)

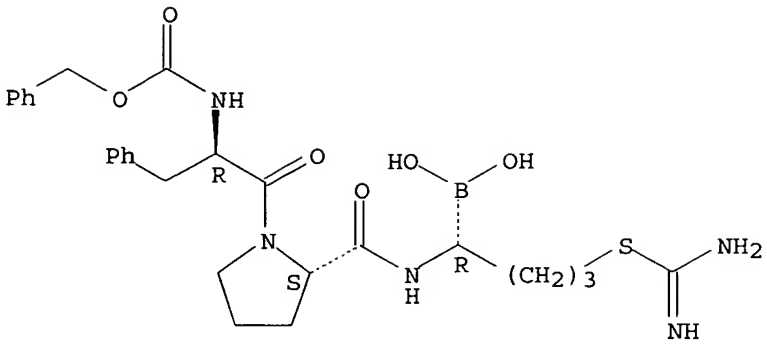
RN 143718-39-2 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-bromobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 176701-90-9 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)thio]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

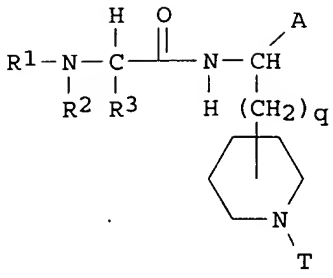


REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

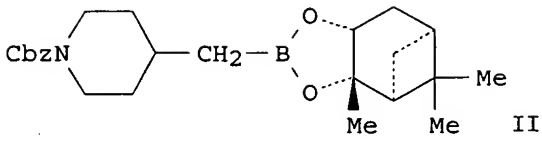
L13 ANSWER 15 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:192155 HCAPLUS
DOCUMENT NUMBER: 128:257688
TITLE: Preparation of piperidine containing aminoboronic acids as trypsin-like serine protease inhibitors
INVENTOR(S): Carini, David John; Cacciola, Joseph; Dominguez, Celia; Fevig, John Matthew
PATENT ASSIGNEE(S): DuPont Merck Pharmaceutical Co., USA
SOURCE: U.S., 12 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5731439	A	19980324	US 1995-409303	19950324
PRIORITY APPLN. INFO.:			US 1995-409303	19950324

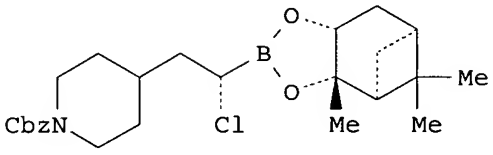
OTHER SOURCE(S): MARPAT 128:257688
GI



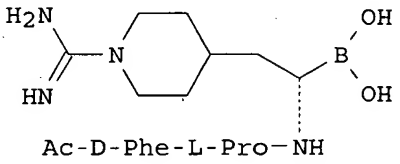
T I



II



III



IV

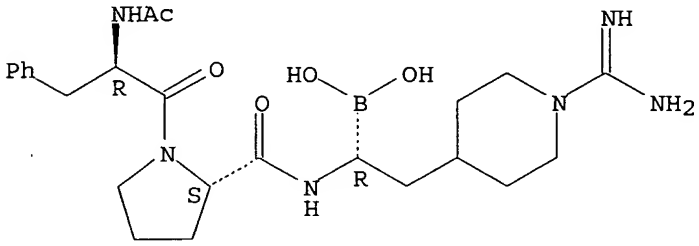
AB The present invention relates generally to α-aminoboronic acids and corresponding peptide analogs I [R1 = COCH[(CH2)nR4]NR5R6, COR8R9-W-(CH2)pR4, CO-C6H4-W-(CH2)tPh, CO-Z-aryl; R2 = CH2C(R12)2-aryl, CH2C(R12)2-heteroaryl, CH2-Z1-aryl, CH2-Z1-heteroaryl; R3 = H; R2R3 = (CH2)3; R4 = H, C1-4 alkyl, aryl, heteroaryl, C3-8 cycloalkyl; R5 = H, C1-4 alkyl, (C1-4 alkyl)-aryl; R6 = COR7, CO2R7, CONR5R7, SO2R7, SO2NR5R7; R7 = C1-4 alkyl, (C1-4 alkyl)-aryl; R8, R9 = independently H, C1-4 alkyl, aryl,(C1-4 alkyl)-aryl; CR8R9 = C3-7 cycloalkyl; R10, R11 = independently H, C1-4 alkyl, (C1-4 alkyl)-aryl, C5-7 cycloalkyl, aryl; NR10R11 = heterocyclic ring; R12 = C1-5 alkyl, C1-5 fluoroalkyl; A = BY1Y2; T = H, C(:NH)NH2,CH:NH; W = bond, O, S(O)qNR5, NCOR7; Y1, Y2 = OR5, F, NR10R11; Y1, Y2 form cyclic boron ester, cyclic boron amide, cyclic boron amide-ester; Z = 1,2-disubstituted C5-7 cycloalkyl, 1,2-disubstituted heterocyclyl; Z1 = 1,1-disubstituted C3-6 cycloalkyl; n = 0, 1; p = 0-3; q = 0-2; s = 1-4; t = 1-3] in which the α-carbon is substituted with an optionally functionalized piperidine containing alkyl group. These compds. are useful as inhibitors of trypsin-like serine protease enzymes. Thus, reaction of protected piperidinylmethylboronate ester II (Cbz = PhCH2O2C) [prepared by addition of catecholborane to N-benzyloxycarbonyl-4-methylenepiperidine and esterification with (+)-pinanediol] with LiCH2Cl gave chloride III, which underwent substitution with LiN(SiMe3)2, peptide coupling with Ac-D-Phe-Pro-OH, hydrogenolysis, guanylation, and deesterification to give desired title compound IV. IV and related prepared aminoboronic acid peptide derivs. exhibited Ki < 20 nM for inhibition of human α-thrombin or human factor Xa.

IT **205127-60-2P 205127-61-3P 205127-62-4P**
205127-63-5P 205127-64-6P 205127-65-7P
205127-66-8P 205127-67-9P 205127-69-1P
205127-70-4P 205127-71-5P 205127-72-6P
205127-73-7P 205127-74-8P 205127-75-9P
205127-76-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of piperidine-containing aminoboronic acids as trypsin-like serine
protease inhibitors)

RN 205127-60-2 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-2-[1-(aminoiminomethyl)-4-piperidinyl]-1-boronoethyl]-, monohydrochloride (9CI) (CA INDEX NAME)

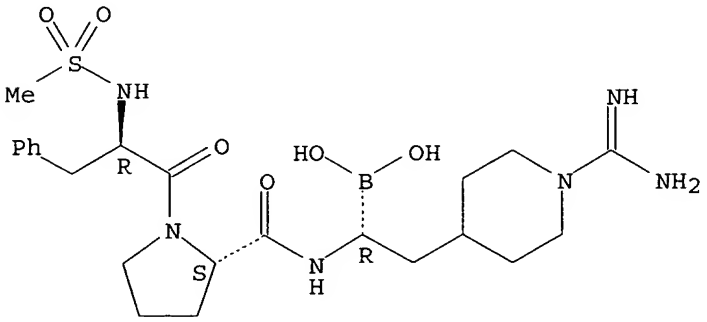
Absolute stereochemistry.



● HCl

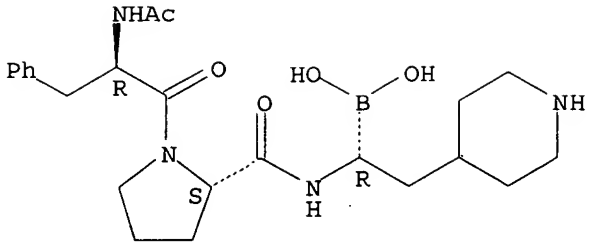
RN 205127-61-3 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[(1R)-2-[1-(aminoiminomethyl)-4-piperidinyl]-1-boronoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



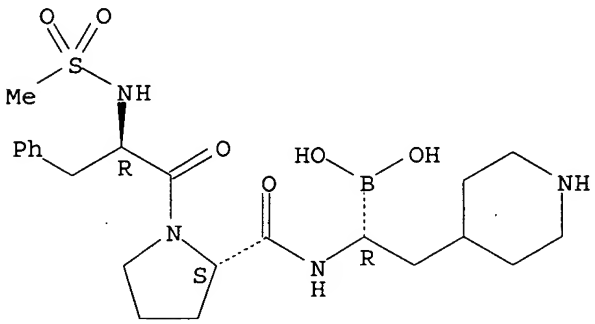
RN 205127-62-4 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-1-borono-2-(4-piperidinyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



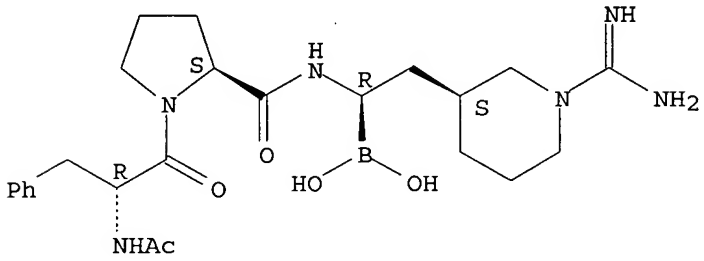
RN 205127-63-5 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[(1R)-1-borono-2-(4-piperidinyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



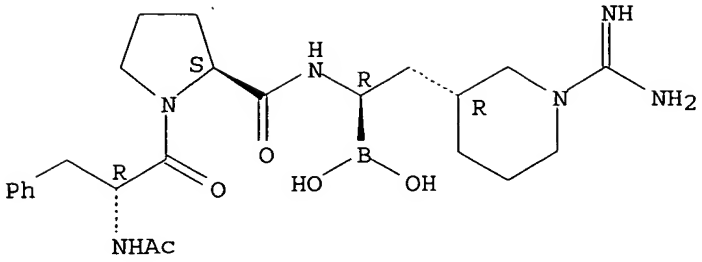
RN 205127-64-6 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-2-[(3S)-1-(aminoiminomethyl)-3-piperidinyl]-1-boronoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



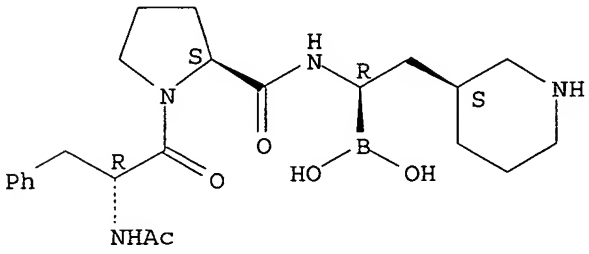
RN 205127-65-7 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-2-[(3R)-1-(aminoiminomethyl)-3-piperidinyl]-1-boronoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



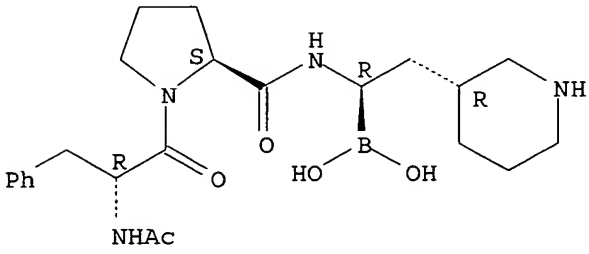
RN 205127-66-8 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-1-borono-2-[(3S)-3-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



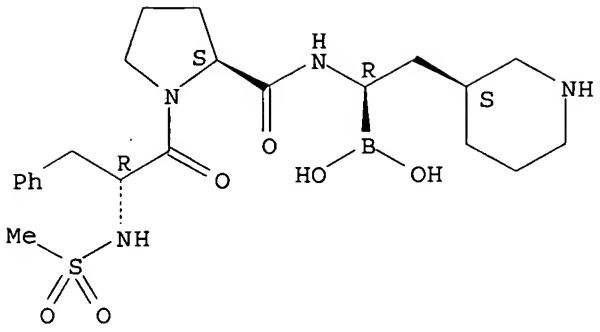
RN 205127-67-9 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-1-borono-2-[(3R)-3-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



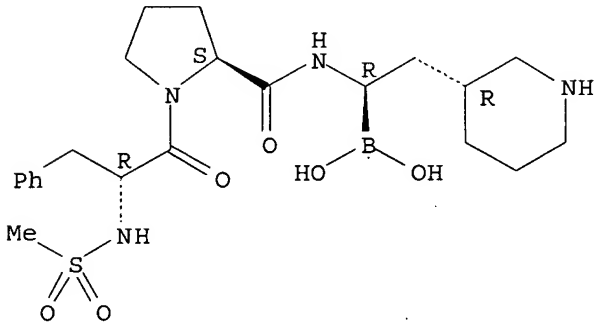
RN 205127-69-1 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[(1R)-1-borono-2-[(3S)-3-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



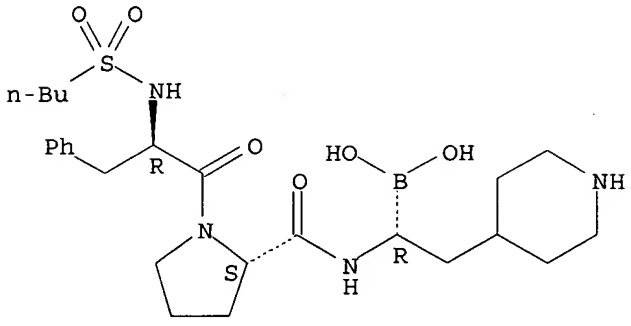
RN 205127-70-4 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[(1R)-1-borono-2-[(3R)-3-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



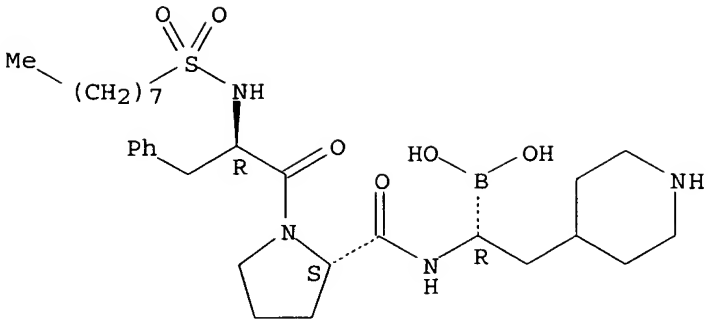
RN 205127-71-5 HCAPLUS
CN L-Prolinamide, N-(butylsulfonyl)-D-phenylalanyl-N-[(1R)-1-borono-2-(4-piperidinyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



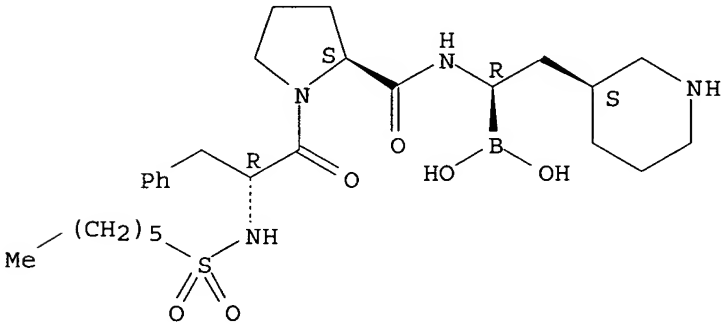
RN 205127-72-6 HCAPLUS
CN L-Prolinamide, N-(octylsulfonyl)-D-phenylalanyl-N-[(1R)-1-borono-2-(4-piperidinyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



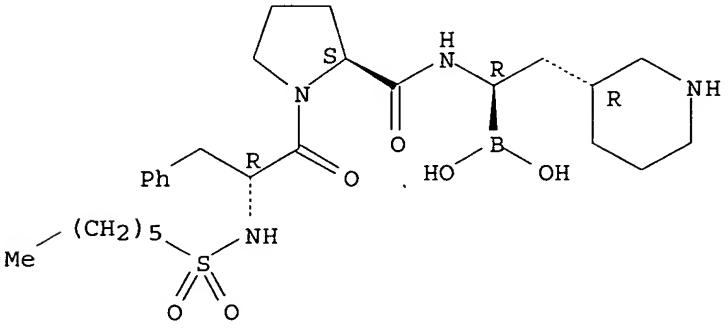
RN 205127-73-7 HCAPLUS
CN L-Prolinamide, N-(hexylsulfonyl)-D-phenylalanyl-N-[(1R)-1-borono-2-[(3S)-3-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



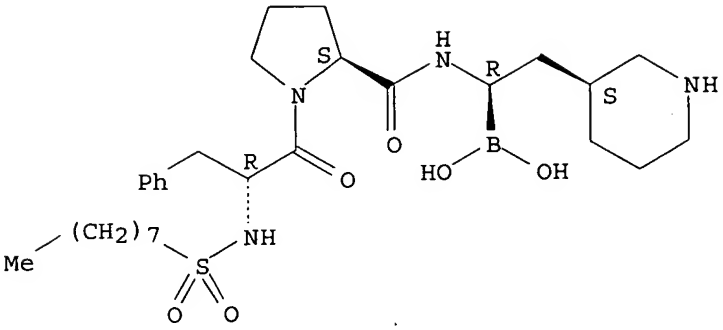
RN 205127-74-8 HCAPLUS
CN L-Prolinamide, N-(hexylsulfonyl)-D-phenylalanyl-N-[(1R)-1-borono-2-[(3R)-3-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



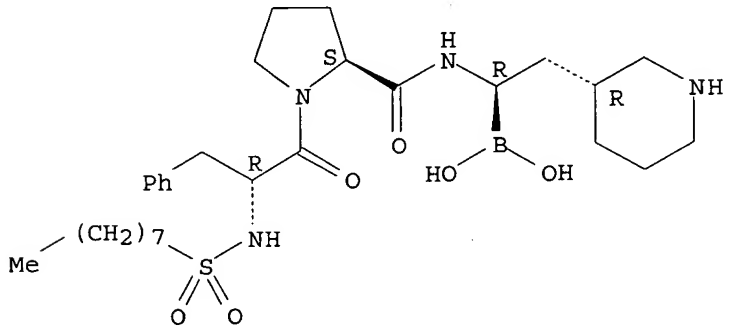
RN 205127-75-9 HCAPLUS
CN L-Prolinamide, N-(octylsulfonyl)-D-phenylalanyl-N-[(1R)-1-borono-2-[(3S)-3-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



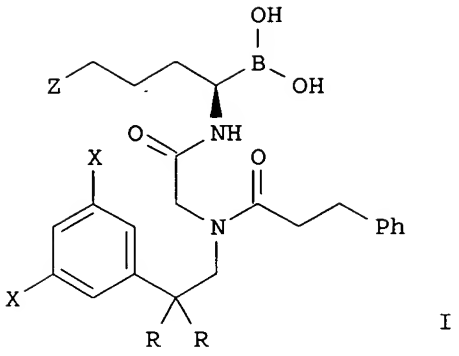
RN 205127-76-0 HCAPLUS
CN L-Prolinamide, N-(octylsulfonyl)-D-phenylalanyl-N-[(1R)-1-borono-2-[(3R)-3-piperidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:131085 HCAPLUS
DOCUMENT NUMBER: 128:217620
TITLE: Rational design of boropeptide thrombin inhibitors: β,β-dialkyl-phenethylglycine P2 analogs of DuP 714 with greater selectivity over complement factor 1 and an improved safety profile
AUTHOR(S): Fevig, John M.; Buriak, Joseph, Jr.; Cacciola, Joseph; Alexander, Richard S.; Kettner, Charles A.; Knabb, Robert M.; Pruitt, James R.; Weber, Patricia C.; Wexler, Ruth R.
CORPORATE SOURCE: The DuPont Merck Pharmaceutical Company, Wilmington, DE, 19880-0500, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1998), 8(3), 301-306
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

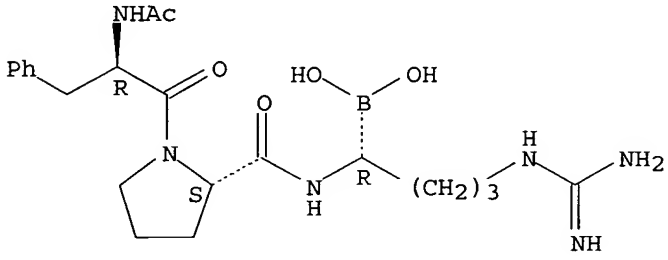
AB The potent boropeptide thrombin inhibitor DuP 714 caused side effects in laboratory animals that appear to be related to its ability to inhibit complement factor I, thereby activating the complement cascade. Using X-ray crystal structure information, the authors have designed boropeptides I [Z = CH2NH2, NHC(:NH)NH2, NHCH:NH; X = H, Me; R = H, Me; RR = (CH2)2, (CH2)4] that have greater selectivity for thrombin over factor I, and also, have reduced tendency to produce these side effects.

IT **130982-43-3**, Dup 714
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(design and biol. activity of boropeptide thrombin inhibitors containing β,β-dialkyl-phenethylglycine)

RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

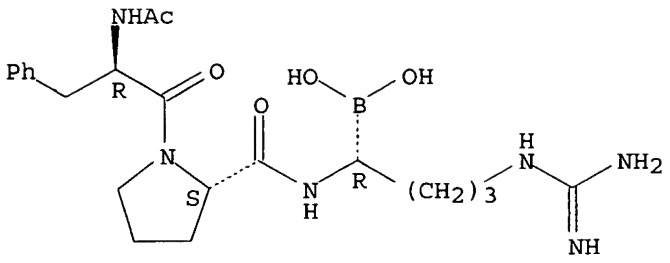


IT **130982-43-3DP**, Dup 714, β,β-dialkyl-phenethylglycine analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(design and biol. activity of boropeptide thrombin inhibitors containing β,β-dialkyl-phenethylglycine)

RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 17 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:671089 HCAPLUS
DOCUMENT NUMBER: 127:341584
TITLE: Selection of S18326 as a new potent and selective boronic acid direct thrombin inhibitor
AUTHOR(S): Rupin, A.; Mennecier, P.; Lila, C.; De Nanteuil, G.; Verbeuren, T. J.
CORPORATE SOURCE: Div. Angiology, Servier Research Inst., Suresnes, F-92150, Fr.
SOURCE: Thrombosis and Haemostasis (1997), 78(4), 1221-1227
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: Schattauer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Using enzymic microassays, the potency of a series of new boroArg tripeptides was determined vs. thrombin and a panel of Ser proteases implicated in the coagulation and fibrinolysis pathways. The inhibition of the Ser protease complement factor I was also studied. Factor I regulates the alternate pathway of the complement and its inhibition appears to be responsible for the toxic effects of the orally available thrombin inhibitor Ac-D-Phe-Pro-boroArg (DuP-714). The structure of the new boronic acid derivs. tested was modified from that of DuP-714 by replacing the proline in the P2 position by N-cycloalkylglycine residues of increasing size (S18989: cyclopropyl; S18563: cyclobutyl; S18326: cyclopentyl; S18229: cyclohexyl). All compds. were found to be slow-tight binding inhibitors of thrombin vs. purified human fibrinogen. Replacement of Pro by N-cycloalkylglycines did not decrease the anti-thrombin potency of the substances up to the cyclopentyl size and this result was confirmed by classical coagulation assays with human plasma in vitro. In contrast, the inhibitory activities of the 4 new boronic acids were found to be lower than those of DuP-714 vs. plasmin, urokinase (u-PA), plasmatic kallikrein, activated protein C (aPC) and complement factor I. The cyclopentyl derivative S18326 is a slightly more active inhibitor of thrombin than DuP-714 (initial IC50 values 3.99 nM vs. 4.73 nM, resp.). Moreover S18326 was identified as the most selective compound of the series with relative potencies being 2-29-fold higher than that of DuP-714 vs. the panel of Ser -proteases tested; the rank order of potency vs. the other Ser proteases for S18326 was t-PA > kallikrein > aPC > factor I > plasmin > fXa > u-PA. These results indicate that the size of the thrombin hydrophobic pocket S2 is sufficient to accept larger residues than Pro in the P2 position of Ac-D-Phe-X-boroArg derivs. while this is not the case for other important Ser proteases of the fibrinolysis, coagulation, and complement pathways. The N-cyclopentyl glycine containing derivative S18326, which is the most potent and the most selective anti-thrombin compound of

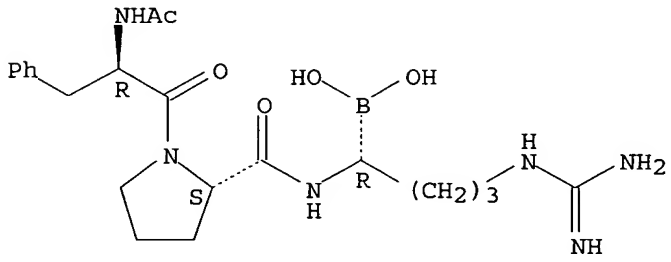
the series, currently undergoes major preclin. testing.

IT **130982-43-3**, Dup 714
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(S18326 potent and selective boronic acid direct thrombin inhibitor)

RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 18 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:643536 HCAPLUS

DOCUMENT NUMBER: 127:328199

TITLE: New Inhibitors of Thrombin and Other Trypsin-like Proteases: Hydrogen Bonding of an Aromatic Cyano Group with a Backbone Amide of the P1 Binding Site Replaces Binding of a Basic Side Chain

AUTHOR(S): Lee, Sheng-Lian; Alexander, Richard; Smallwood, Angela; Trievel, Raymond; Mersinger, Lawrence; Weber, Patricia C.; Kettner, Charles

CORPORATE SOURCE: Chemical and Physical Sciences DuPont Experimental Station, DuPont Merck Pharmaceutical Company, Wilmington, DE, 19880-0500, USA

SOURCE: Biochemistry (1997), 36(43), 13180-13186
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

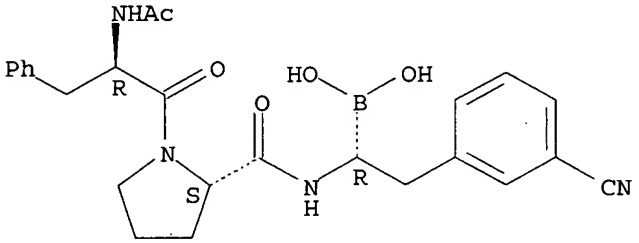
AB Highly effective thrombin inhibitors have been obtained by preparing boronic acid analogs of m-cyano-substituted phenylalanine and its incorporation into peptides. The cyano group enhances binding by several orders of magnitude. For example, Ac-(D)Phe-Pro-boroPheOH binds to thrombin with a Ki of 320 nM and the Ki of Ac-(D)Phe-Pro-boroPhe(m-CN)-OH is 0.79 nM. Protein crystal structure determination of trypsin complexed to H-(D)Phe-Pro-boroPhe(m-CN)-OH indicates that the aromatic side chain is bound in the P1 binding site and that the cyano group can act as a H-bond acceptor for the amide proton of Gly219. Enhanced binding for inhibitors containing the m-cyano group was observed for coagulation factor Xa and for the factor VIIa·tissue factor complex [Ki values of Ac-(D)Phe-Pro-boroPhe(mCN)-OH are 760 and 3.3 nM, resp.]. This result is consistent with the sequence homol. of these two enzymes in the P1 binding site. Two enzymes lacking the strict homol. in the P1 binding site, pancreatic kallikrein and chymotrypsin, did not exhibit significantly enhanced binding.

IT **197913-52-3 197913-54-5**

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of new inhibitors of thrombin and other trypsin-like proteases and hydrogen bonding of aromatic cyano group in P1 binding site)

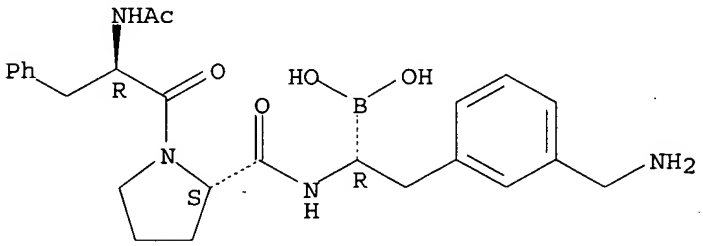
RN 197913-52-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-1-borono-2-(3-cyanophenyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 197913-54-5 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-2-[3-(aminomethyl)phenyl]-1-boronoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 19 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:594514 HCAPLUS
DOCUMENT NUMBER: 127:234621
TITLE: Amidino and guanidino substituted boronic acid inhibitors of trypsin-like enzymes
INVENTOR(S): Lee, Sheng-lian O.; Carini, David John; Fevig, John Matthew; Kettner, Charles Adrian; Mantri, Padmaja; Feng, Zixia
PATENT ASSIGNEE(S): Dupont Merck Pharmaceutical Co., USA
SOURCE: U.S., 45 pp., Cont.-in-part of U. S. Ser. No. 204,055, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5658885	A	19970819	US 1994-329039	19941025
ZA 9402899	A	19951026	ZA 1994-2899	19940426
CA 2200192	AA	19960502	CA 1995-2200192	19951024
CA 2200192	C	20010116		
WO 9612499	A1	19960502	WO 1995-US13702	19951024
W: AU, CA, JP, MX, NZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9539671	A1	19960515	AU 1995-39671	19951024
EP 787010	A1	19970806	EP 1995-937612	19951024
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 10508010	T2	19980804	JP 1995-514116	19951024
PRIORITY APPLN. INFO.:			US 1993-52835 B2	19930427
			US 1994-204055 B2	19940302
			US 1994-329039 A	19941025
			WO 1995-US13702 W	19951024

OTHER SOURCE(S): MARPAT 127:234621

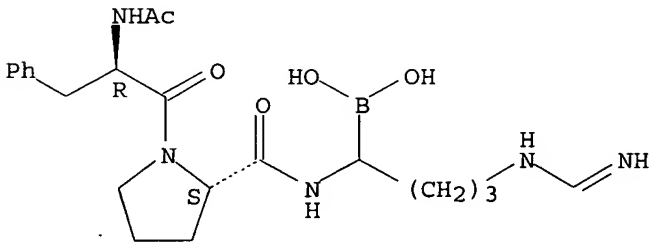
AB Title boronic acids R3XnNR2CHR1BR4R5 [X = amino acid or peptide residue; n = 0, 1; R1 = guanidino- or aminoxy-substituted alkyl, substituted Ph, phenylalkyl, cycloalkyl, or cycloalkylalkyl; R2 = H, (un)substituted alkyl, cycloalkyl, aryl, alkylaryl; R3 = H, alkyl, aryl, alkylaryl, NH2 blocking group, etc.; R4, R5 = OH or taken together form a cyclic boronate ester] were prepared as inhibitors of trypsin-like enzymes. Thus, Ac-D-Phe-Pro-NHCH[(CH2)4CN]BO2C10H16 was prepared by coupling of Ac-D-Phe-Pro-OH with H2N-CH[(CH2)4Br]BO2C10H16.HCl, followed by cyanation. The product inhibited thrombin with Ki of <50,000 nM.

IT **167088-06-4P 167088-24-6P 167088-25-7P**
167088-26-8P 167088-27-9P 167088-44-0P
167088-45-1P 167088-49-5P 167088-50-8P
167088-51-9P 167088-52-0P 179614-17-6P
179614-31-4P 179614-32-5P 194987-35-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amidino and guanidino substituted boronic acid inhibitors of trypsin-like enzymes)

RN 167088-06-4 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]- (9CI) (CA INDEX NAME)

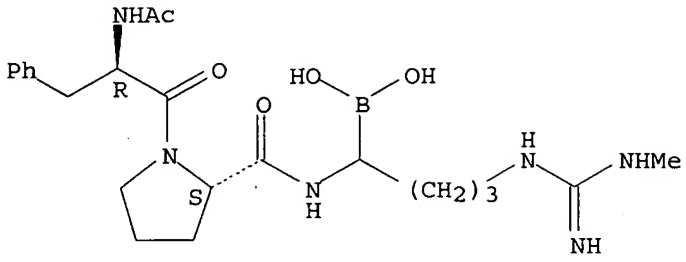
Absolute stereochemistry.



RN 167088-24-6 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

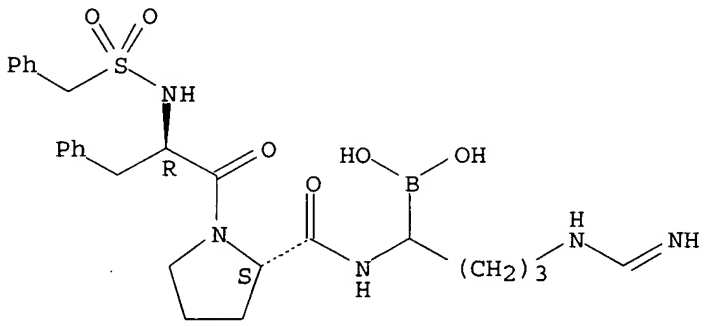
Absolute stereochemistry.



● HCl

RN 167088-25-7 HCAPLUS
CN L-Prolinamide, N-[(phenylmethyl)sulfonyl]-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

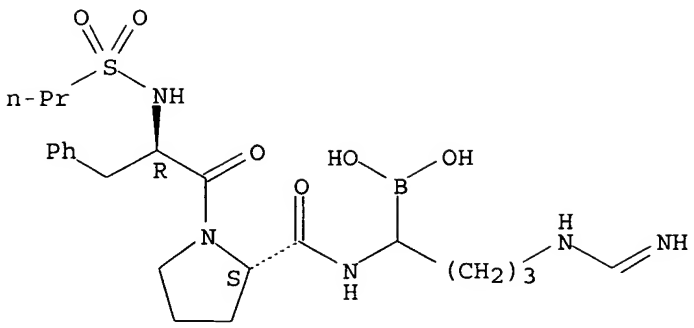
Absolute stereochemistry.



● HCl

RN 167088-26-8 HCAPLUS
CN L-Prolinamide, N-(propylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

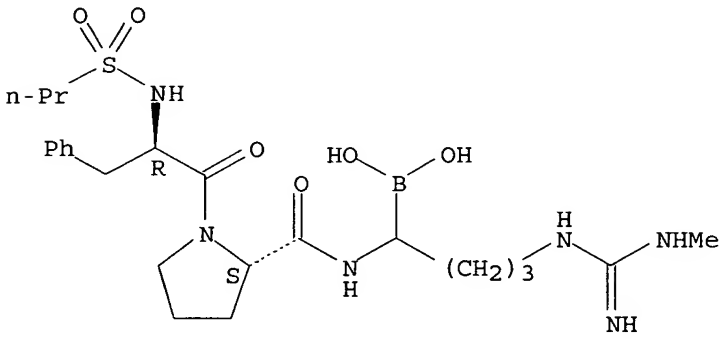
Absolute stereochemistry.



● HCl

RN 167088-27-9 HCAPLUS
CN L-Prolinamide, N-(propylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

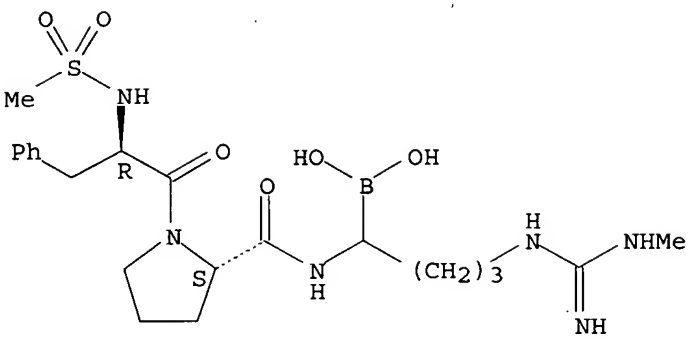
Absolute stereochemistry.



● HCl

RN 167088-44-0 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

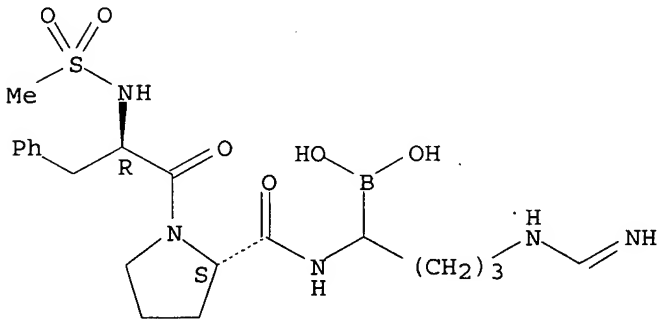
Absolute stereochemistry.



● HCl

RN 167088-45-1 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

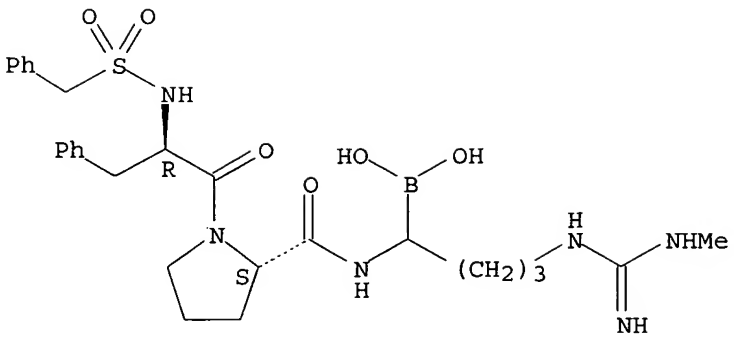
Absolute stereochemistry.



● HCl

RN 167088-49-5 HCAPLUS
CN L-Prolinamide, N-[(phenylmethyl)sulfonyl]-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

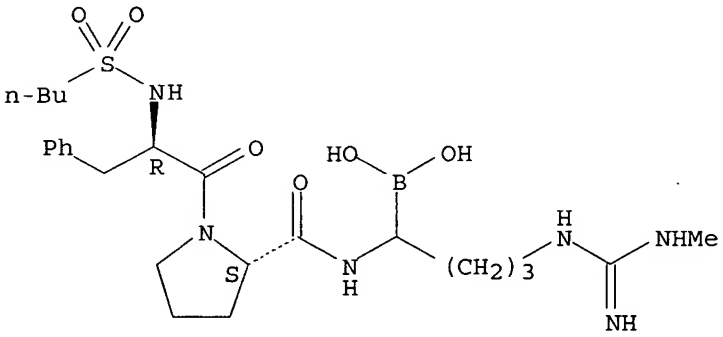
Absolute stereochemistry.



● HCl

RN 167088-50-8 HCAPLUS
CN L-Prolinamide, N-(butylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

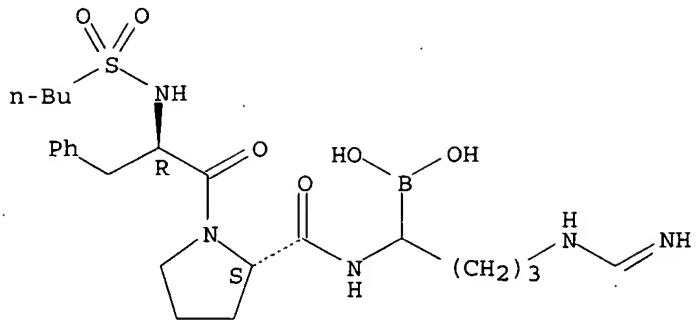
Absolute stereochemistry.



● HCl

RN 167088-51-9 HCAPLUS
CN L-Prolinamide, N-(butylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

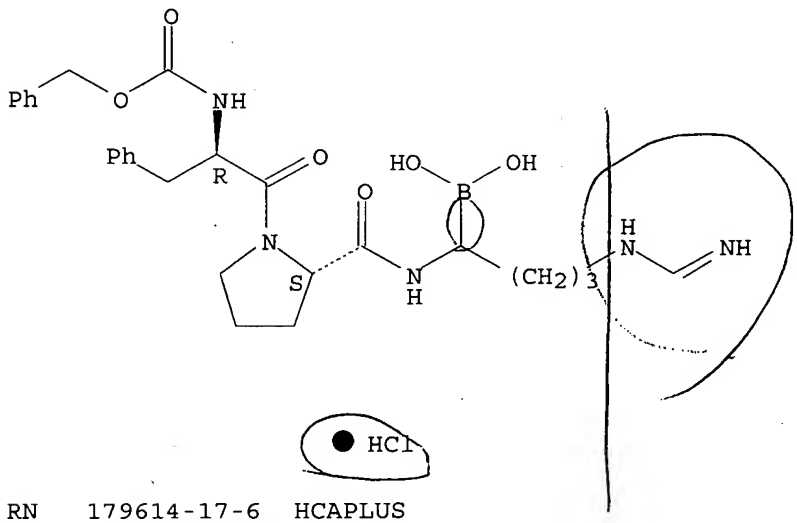
Absolute stereochemistry.



● HCl

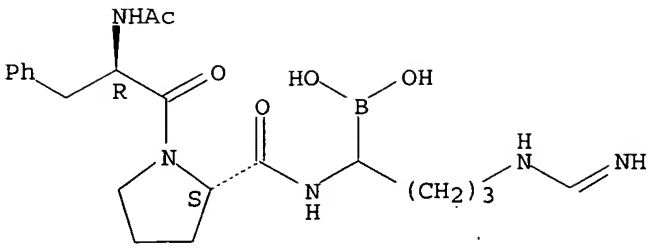
RN 167088-52-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 179614-17-6 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

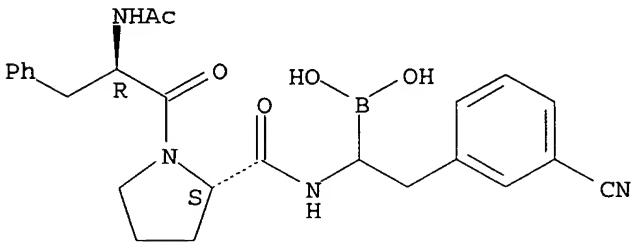
Absolute stereochemistry.



● HCl

RN 179614-31-4 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-2-(3-cyanophenyl)ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)

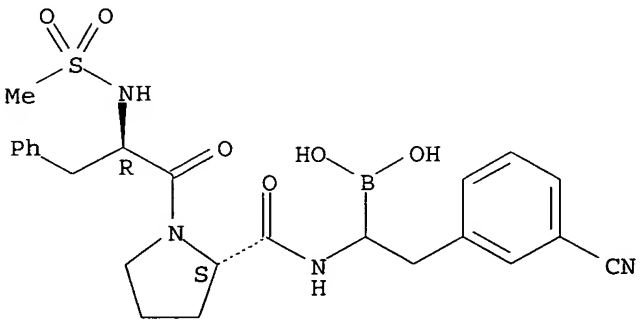
Absolute stereochemistry.



● HCl

RN 179614-32-5 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[1-borono-2-(3-cyanophenyl)ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)

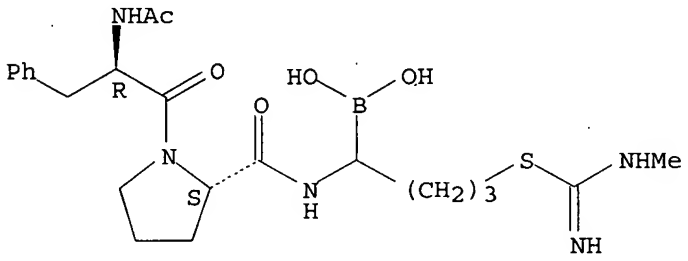
Absolute stereochemistry.



● HCl

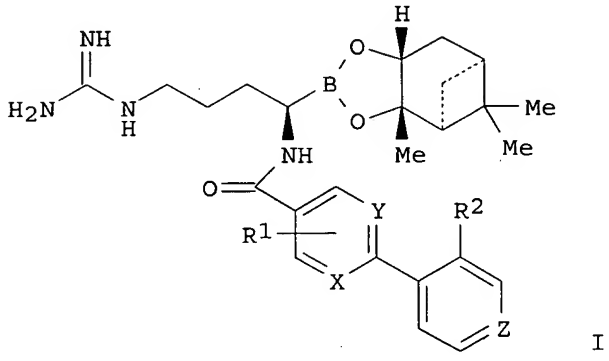
RN 194987-35-4 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]thio]butyl]-, monohydrobromide (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HBr

L13 ANSWER 20 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:468966 HCAPLUS
DOCUMENT NUMBER: 127:162100
TITLE: Biaryl substituted alkylboronate esters as thrombin inhibitors
AUTHOR(S): Quan, M. L.; Wityak, J.; Dominguez, C.; Duncia, J. V.; Kettner, C. A.; Ellis, C. D.; Liauw, A. Y.; Park, J. M.; Santella, J. B.; Knabb, R. M.; Thoolen, M. J.; Weber, P. C.; Wexler, R. R.
CORPORATE SOURCE: The DuPont Merck Pharmaceutical Company, Wilmington, DE, 19880-0500, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1997), 7(13), 1595-1600
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

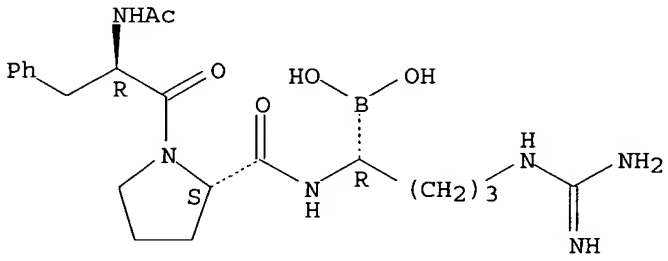
AB Thrombin is a serine protease that plays an important role in the blood coagulation cascade, and is a target enzyme for new therapeutic agents. Ac-D-Phe-Pro-boroArg-OH (DuP 714) is a highly effective thrombin inhibitor. In order to reduce the peptidic nature of DuP 714, a series of novel biaryl substituted alkylboronate esters, e.g. I (R1 = H, 2-Me, 2-F, 2-NH2, 2-NO2, 3-NO2, 3-NH2; R2 = H, SO2NHCMe3, SO2NEt2, CF3, SO2NH2, SO2NHCO2Me; X, Y, Z = independently CH, N) was designed as potent thrombin inhibitors. The most potent compds. have subnanomolar affinity for thrombin.

IT **130982-43-3DP**, DuP 714, alkylboronate ester analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and activity of of biaryl-substituted alkylboronate ester analogs of boroarginine thrombin inhibitor DuP 714)

RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

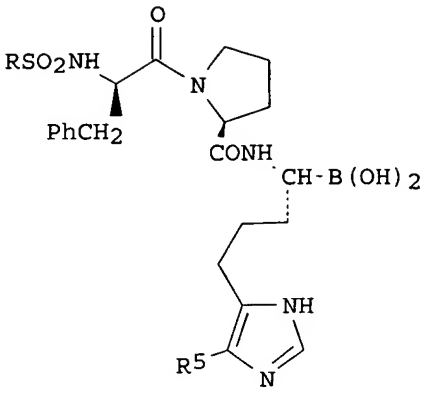


REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 21 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:457067 HCAPLUS
DOCUMENT NUMBER: 127:95617
TITLE: N-sulfonyl and N-sulfamoyl peptidyl prolinamide derivatives
INVENTOR(S): Mallart, Sergio; Lassalle, Gilbert; Bellevergue, Patrice
PATENT ASSIGNEE(S): Synthelabo S. A., Fr.
SOURCE: Fr. Demande, 37 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2739858	A1	19970418	FR 1995-11904	19951011
FR 2739858	B1	19971114		
PRIORITY APPLN. INFO.:			FR 1995-11904	19951011

OTHER SOURCE(S): MARPAT 127:95617
GI



I

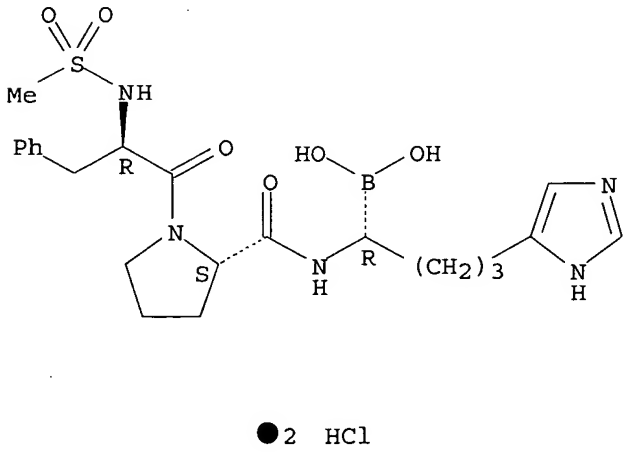
AB Title prolinamide derivs. I [R = alkyl, phenylalkyl, R1R2N (R1 = H, alkyl, phenylalkyl and R2 = alkyl, phenylalkyl), 1-pyrrolidinyl, 1-piperidinyl, morpholino, etc.; R5 = H, alkyl] or their isomers were prepared for use as antithrombotics. Thus, (R)-N-(methylsulfonyl)-D-phenylalanyl-N-[1-borono-4-(1H-imidazol-4-yl)butyl]-L-prolinamide was prepared via coupling of N-[(1,1-dimethylethoxy)carbonyl]-N-(methylsulfonyl)-D-phenylalanyl-L-proline with (R)-α-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-imidazole-4-butanamine.

IT **191992-65-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(N-sulfonyl and N-sulfamoyl peptidyl prolinamide derivs.)

RN 191992-65-1 HCAPLUS

CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[(1R)-1-borono-4-(1H-imidazol-4-yl)butyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



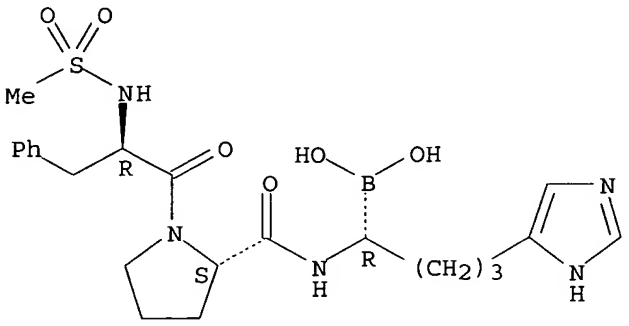
●2 HCl

IT **191992-66-2P 191992-67-3P 191992-72-0P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(N-sulfonyl and N-sulfamoyl peptidyl prolinamide derivs.)

RN 191992-66-2 HCAPLUS

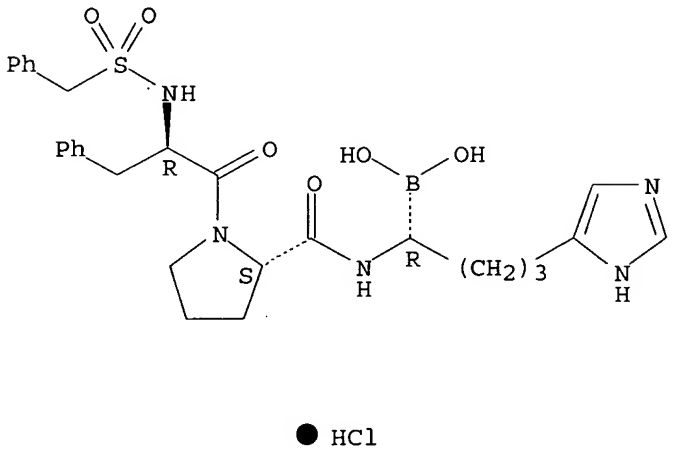
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[(1R)-1-borono-4-(1H-imidazol-4-yl)butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 191992-67-3 HCAPLUS
CN L-Prolinamide, N-[(phenylmethyl)sulfonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-(1H-imidazol-4-yl)butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

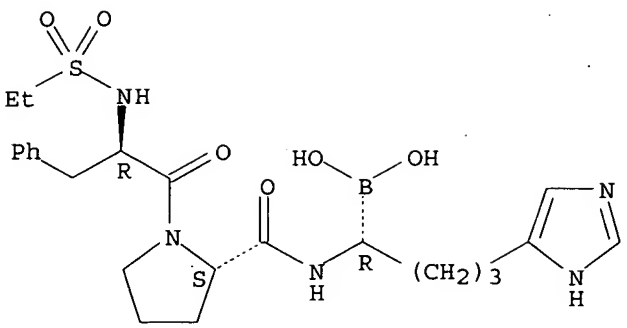
Absolute stereochemistry. Rotation (-).



● HCl

RN 191992-72-0 HCAPLUS
CN L-Prolinamide, N-(ethylsulfonyl)-D-phenylalanyl-N-[(1R)-1-borono-4-(1H-imidazol-4-yl)butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● HCl

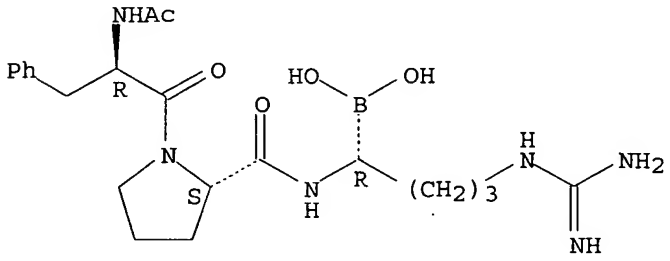
L13 ANSWER 22 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:643302 HCAPLUS
DOCUMENT NUMBER: 125:316708
TITLE: Comparative anticoagulant effects of various thrombin inhibitors, as determined in the ecarin clotting time method
AUTHOR(S): Callas, Demetra D.; Fareed, Jawed
CORPORATE SOURCE: Dep. Pathol., Loyola Univ. Chicago, Maywood, IL, 60153, USA
SOURCE: Thrombosis Research (1996), 83(6), 463-468
CODEN: THBRAA; ISSN: 0049-3848
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recombinant and synthetic inhibitors of thrombin such as hirudin, efetran and argatroban are in various phases of clin. trials in several surgical and medical indications (1,2). The therapeutic effects of these agents are usually monitored by activated partial thromboplastin time (APTT) whereas in cardiovascular indications the whole blood activated clotting time (ACT) is used (1,3). The reliability of both the APTT and the ACT in predicting the safety of various thrombin inhibitors has been heavily debated (3,4,5). Furthermore, some of the inhibitors may be administered simultaneously to heparinized and coumadinized patients and the obtained APTT and ACT results may not truly reflect the effects of these agents. Ecarin is a snake venom enzyme derived from the viper Echis carinatus, with converts prothrombin into meizothrombin and other intermediates, targeting the Arg320-Ile320-Ile321 bond between the A and B chains of prothrombin (6). These thrombin intermediates exhibit clotting activity, although not as potent as fully formed α thrombin. While thrombin inhibitors are capable of inhibiting these thrombin intermediates, antithrombin III (AT-III) has no effect and consequently neither does heparin. Using purified ecarin, Nowak and Bucha (6,7) proposed a whole blood and plasma based clotting assay, the ecarin clotting time, to monitor hirudin's anticoagulant effects. Since the other thrombin inhibitors also interact directly with thrombin, various antithrombin agents were compared in ecarin clotting time to test its diagnostic efficacy.

IT **130982-43-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

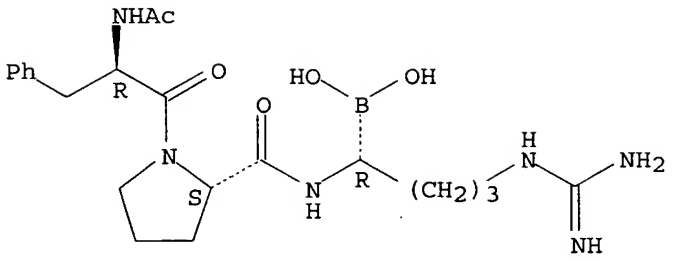
(Uses)
(comparative anticoagulant effects of various thrombin inhibitors, as determined in ecarin clotting time method)
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 23 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:533708 HCAPLUS
DOCUMENT NUMBER: 125:212229
TITLE: Comparative studies on the antithrombin potency of various thrombin inhibitors, as determined by using an amidolytic method
AUTHOR(S): Callas, Demetra D.; Fareed, Jawed
CORPORATE SOURCE: Department of Pharmacology, Loyola University Chicago, Maywood, IL, 60153, USA
SOURCE: Thrombosis Research (1996), 83(1), 97-102
CODEN: THBRAA; ISSN: 0049-3848
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors utilized an amidolytic method for the determination of the antithrombin potency of several thrombin inhibitors. On a gravimetric basis, the most potent thrombin inhibitor appeared to be Ac-(D)Phe-Pro-boroArg-OH (DuP 714) followed by the aldehydes D-Phe-Pro-Arg-H (GYKI 14166) and D-MePhe-Pro-Arg-H (GYKI 14766) (LY294468) (efegatran sulfate) and then by Boc-D-Phe-Pro-Arg-H (GYKI 14451) and hirudin followed by argatroban. When the specific activity was expressed in terms of antithrombin unit potency, the order of potency was hirudin followed by Ac-(D)Phe-Pro-boroArg-OH, D-Phe-Pro-Arg-H and D-MePhe-Pro-Arg-H, Boc-D-Phe-Pro-Arg-H and argatroban. The clin. use of these agents is discussed.
IT **130982-43-3**, DuP 714
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparative studies on antithrombin potency of various thrombin inhibitors as determined by using amidolytic method)
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

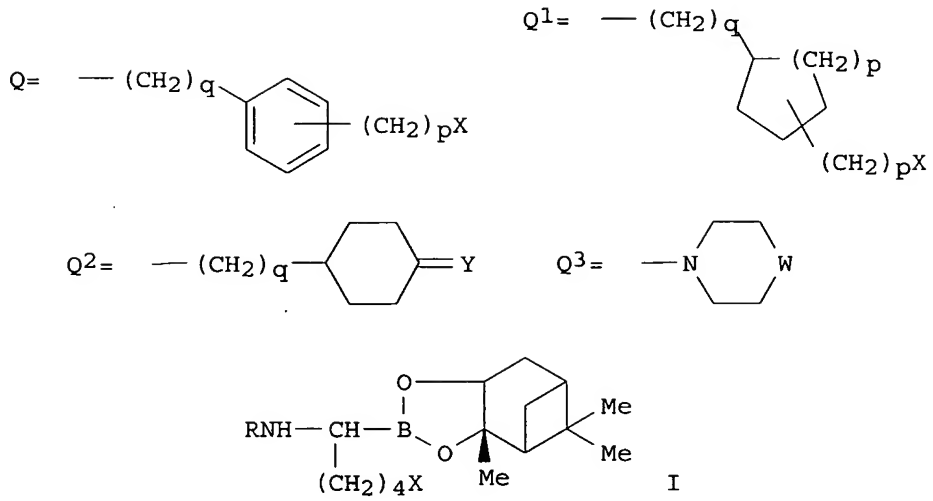
Absolute stereochemistry.



L13 ANSWER 24 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:476626 HCAPLUS
DOCUMENT NUMBER: 125:143313
TITLE: Preparation of amidino and guanidino substituted peptide analogs as inhibitors of trypsin-like enzymes
INVENTOR(S): Lee, Sheng-lian O.; Carini, David John; Fevig, John Matthew; Kettner, Charles Adrian; Mantri, Padmaja; Feng, Zixia
PATENT ASSIGNEE(S): Du Pont Merck Pharmaceutical Company, USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9612499	A1	19960502	WO 1995-US13702	19951024
W: AU, CA, JP, MX, NZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5658885	A	19970819	US 1994-329039	19941025
AU 9539671	A1	19960515	AU 1995-39671	19951024
EP 787010	A1	19970806	EP 1995-937612	19951024
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 10508010	T2	19980804	JP 1995-514116	19951024
PRIORITY APPLN. INFO.:			US 1994-329039 A	19941025
			US 1993-52835 B2	19930427
			US 1994-204055 B2	19940302
			WO 1995-US13702 W	19951024

OTHER SOURCE(S): MARPAT 125:143313
GI



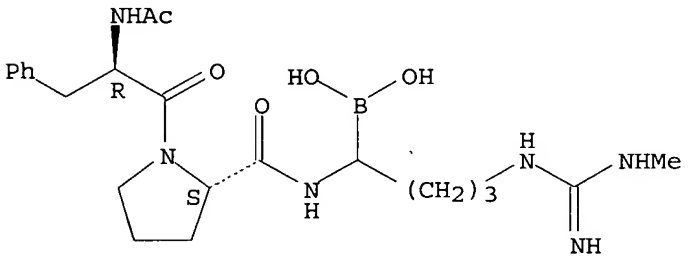
AB Novel α-amino acid and α-aminoboronic acid and corresponding peptide analogs of formula R3[A]nNR2CHR1E [E = BY1Y2, COR14, CO2R4, CONR15R16, COR4, COCO2R4; wherein Y1, Y2 = OH, F, (un)substituted NH2; or Y1Y2 = cyclic boron ester, cyclic boron amide, or cyclic boron amide-ester containing 2-20 carbon atoms and optionally 1-3 heteroatoms selected from N, S, and O; R4 = H, C1-4 alkyl, aryl-C1-4 alkyl, C5-7 cycloalkyl; R14 = CF3, CHF2, CH2F, CH2Cl, CO2R4, CONR15R16, COR4, etc.; R15, R16 = H, C1-4 alkyl, aryl-C1-4 alkyl, C5-7 cycloalkyl, (un)substituted Ph; or NR15R16 = Q3; wherein W = single bond, O, S, SO, SO2, CH2, NR4, NCOR4; R1 = (un)substituted C1-12 alkyl, Q, Q1; wherein X = halo, cyano, NO2, CF3, NH2, NHC(:NH)H, NHC(:NH)NHOH, NHC(:NH)NHCN, etc.; Y = O, :NOH, :NNHCHO; p = 0-3; q = 0-4; R2 = H, (un)substituted C1-12 alkyl, cycloalkyl, Ph, naphthyl, or aryl-C1-4 alkyl; R3 = H, alkyl, aryl, alkylaryl, S(O)rR7, COR7, CO2R7, P(O)2OR7, or any other C1-20 NH2-blocking group; wherein R7 = H, C1-4 alkyl, (un)substituted Ph, naphthyl, or aryl-C1-4 alkyl; r = 0-2; A = amino acid residue or peptide comprised of 2-20 amino acids residue; n = 0,1] and pharmaceutically acceptable salts thereof are prepared These peptide analogs are useful for treating a physiol. disorder in a warm blooded animal catalyzed by trypsin-like enzymes, e.g. blood clotting, arterial thrombosis, myocardial infarction, inflammation, pancreatitis, and hereditary angioedema. Trypsin-like enzymes are a group of proteases which hydrolyze peptide bonds at basic residues liberating either a C-terminal arginyl or lysyl residue, among which are enzymes of the blood coagulation and fibrinolytic system required for hemostasis (e.g. factors II, X, VII, IX, kallikrein, tissue plasminogen activators, urokinase-like plasminogen activator, and plasmin), enzymes of the complement system, acrosin, and pancreatic trypsin. Thus, Ac-D-Phe-Pro-OH was condensed with a boronic acid derivative (I; R = H, X = Br) by a mixed anhydride procedure using iso-Bu chloroformate and N-methylmorpholine in CCl4 to give an intermediate I (R = Ac-D-Phe-Pro, X = Br), which was heated with Bu4NCN in MeCN at 90° for 3 h to give the nitrile I (R = Ac-D-Phe-Pro, X = cyano). The latter nitrile was stirred with saturated methanolic HCl at 4° overnight, concentrated, and redissolved in MeOH. NH3(g) was bubbled through the solution for 1 h and the solution was heated at 50° for 3 h to give I [R = Ac-D-Phe-Pro, X = C(:NH)NH2]. This compound in vitro inhibited thrombin with Ki of <500 nM.

IT **167088-24-6P 167088-25-7P 167088-26-8P 167088-27-9P 167088-44-0P 167088-45-1P**

167088-49-5P 167088-50-8P 167088-51-9P
167088-52-0P 179614-17-6P 179614-31-4P
179614-32-5P 179614-51-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amidino and guanidino substituted peptide analogs containing α-aminoboronic acid as inhibitors of trypsin-like enzymes for disease therapy)

RN 167088-24-6 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

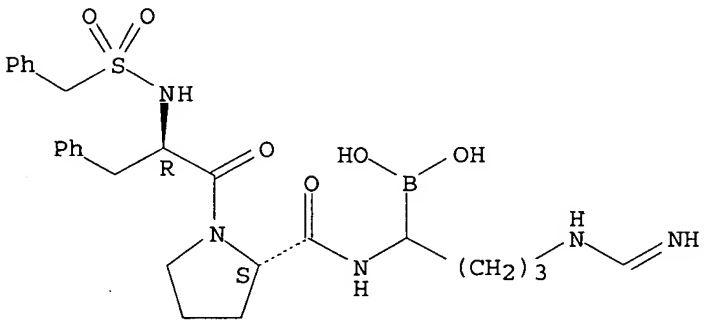
Absolute stereochemistry.



● HCl

RN 167088-25-7 HCAPLUS
CN L-Prolinamide, N-[(phenylmethyl)sulfonyl]-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

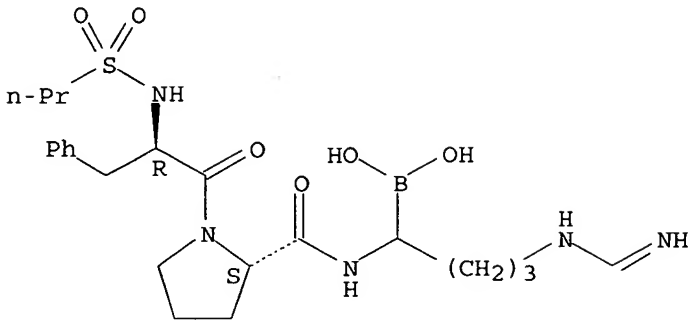
Absolute stereochemistry.



● HCl

RN 167088-26-8 HCAPLUS
CN L-Prolinamide, N-(propylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

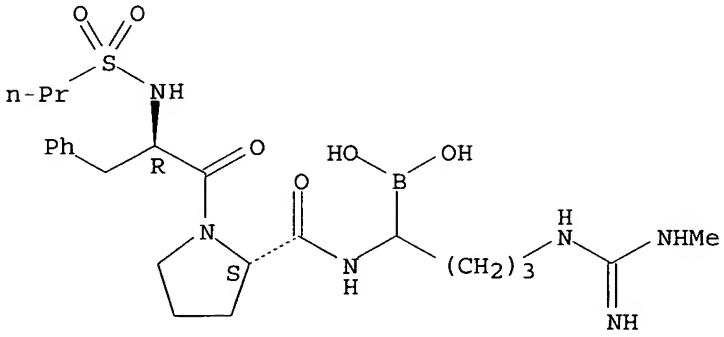
Absolute stereochemistry.



● HCl

RN 167088-27-9 HCAPLUS
CN L-Prolinamide, N-(propylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

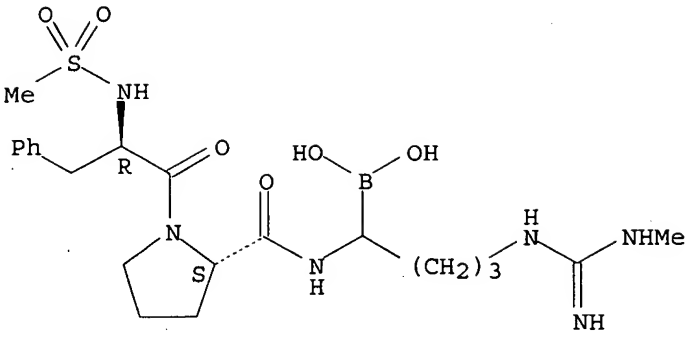
Absolute stereochemistry.



● HCl

RN 167088-44-0 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

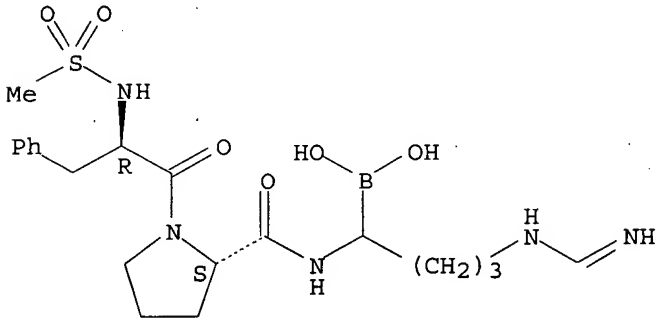
Absolute stereochemistry.



● HCl

RN 167088-45-1 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

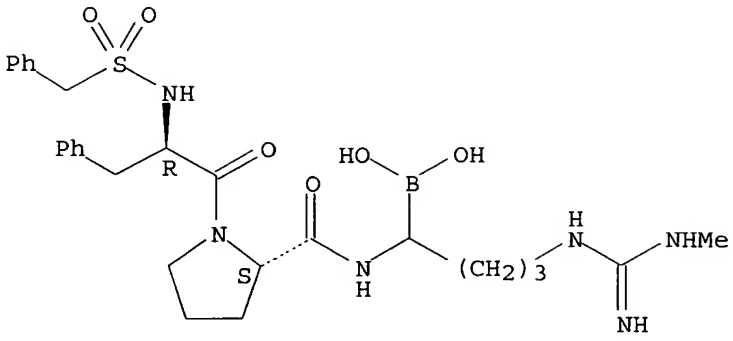
Absolute stereochemistry.



● HCl

RN 167088-49-5 HCAPLUS
CN L-Prolinamide, N-[(phenylmethyl)sulfonyl]-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

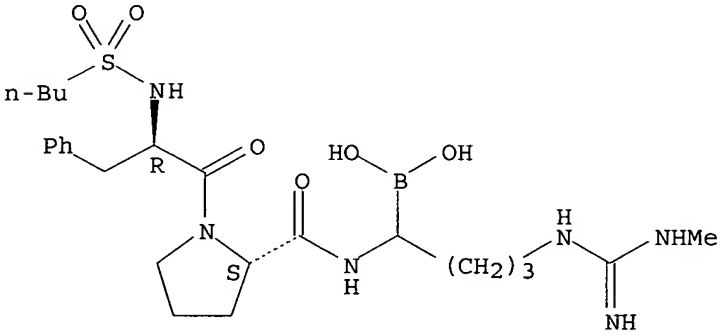
Absolute stereochemistry.



● HCl

RN 167088-50-8 HCAPLUS
CN L-Prolinamide, N-(butylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

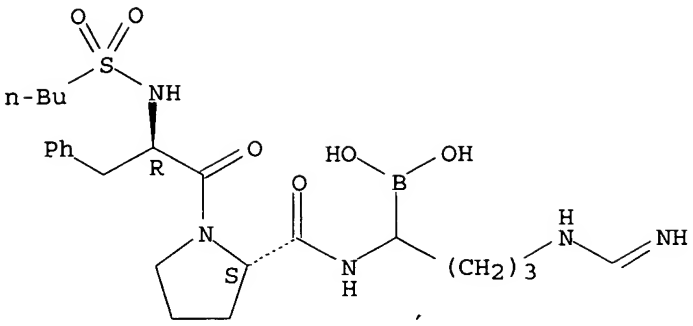
Absolute stereochemistry.



● HCl

RN 167088-51-9 HCAPLUS
CN L-Prolinamide, N-(butylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

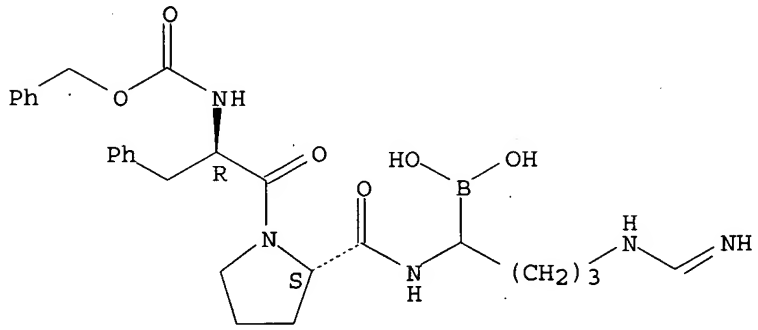
Absolute stereochemistry.



● HCl

RN 167088-52-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

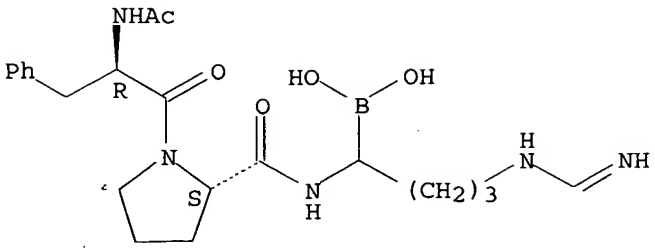
Absolute stereochemistry.



● HCl

RN 179614-17-6 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

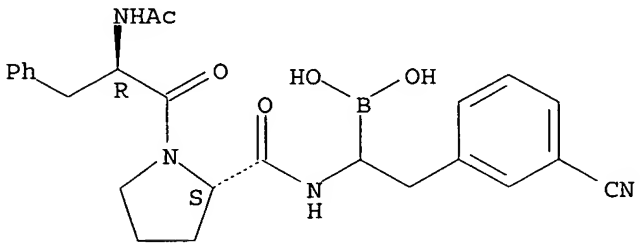
Absolute stereochemistry.



● HCl

RN 179614-31-4 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-2-(3-cyanophenyl)ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)

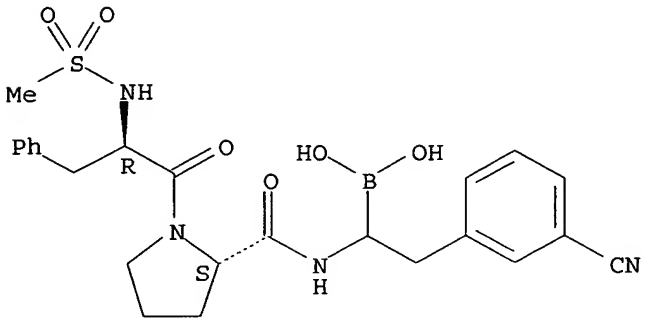
Absolute stereochemistry.



● HCl

RN 179614-32-5 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[1-borono-2-(3-cyanophenyl)ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)

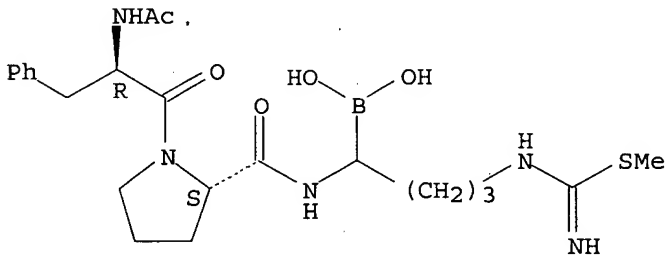
Absolute stereochemistry.



● HCl

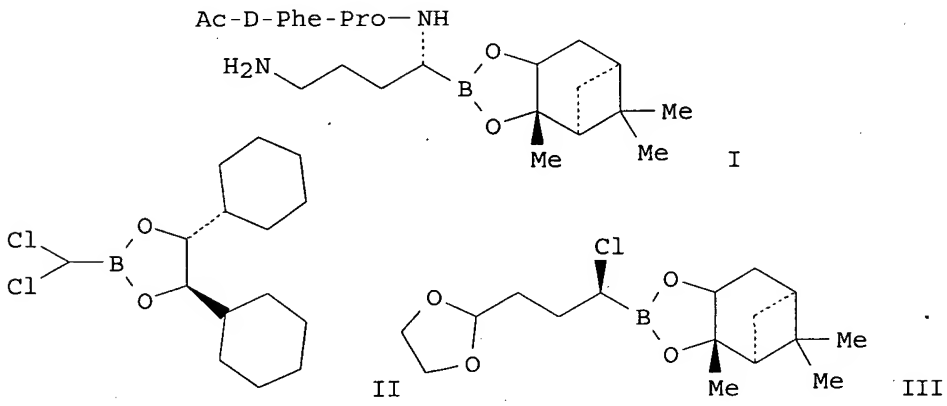
RN 179614-51-8 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-[[imino(methylthio)methyl]amino]butyl]-, monohydrobromide (9CI) (CA INDEX NAME),

Absolute stereochemistry.



● HBr

L13 ANSWER 25 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:440882 HCAPLUS
DOCUMENT NUMBER: 125:222393
TITLE: New Asymmetric Synthesis of α-Aminoboronic Acids Containing Functionalized Side Chains
AUTHOR(S): Mantri, Padmaja; Duffy, Daniel E.; Kettner, Charles A.
CORPORATE SOURCE: DuPont Merck Pharmaceutical Company, Wilmington, DE, 19880-0500, USA
SOURCE: Journal of Organic Chemistry (1996), 61(16), 5690-5692
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 125:222393
GI



AB A new method for the preparation of boroornithine peptide I, a key intermediate in the preparation of thrombin inhibitor DuP 714, in 35% overall yield under

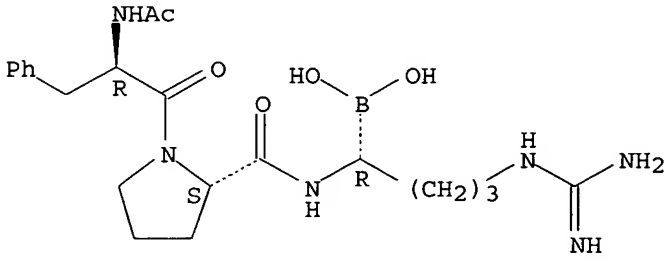
conditions amenable for large scale synthesis is given. The key step is the stereoselective substitution of 2-(2-dioxolanyl)ethylmagnesium bromide with (R,R)-1,2-dicyclohexylethanediol dichloromethylboronic ester II and subsequent transesterification with (+)-pinanediol to give III.

IT **130982-43-3P**, DuP 714
RL: SPN (Synthetic preparation); PREP (Preparation)
(asym. synthesis of aminoboronic acids containing functionalized side chains)

RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 26 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:404693 HCAPLUS

DOCUMENT NUMBER: 125:52248

TITLE: Structure-Based Understanding of Ligand Affinity Using Human Thrombin as a Model System

AUTHOR(S): Nienaber, Vicki L.; Mersinger, Lawrence J.; Kettner, Charles A.

CORPORATE SOURCE: Department of Chemical and Physical Sciences, DuPont Merck Pharmaceutical Company, Wilmington, DE, 19880, USA

SOURCE: Biochemistry (1996), 35(30), 9690-9699
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Kinetic study of a series of compds. containing the thrombin-directed peptide D-Phe-Pro-boroArg-OH had indicated that the structure of the N-terminal blocking group may be correlated with binding [Kettner, C., Mersinger, L., & Knabb, R. (1990) J. Biol. Chemical 265, 18289-18297]. To further study this phenomenon, a second series of compds. that contains a C-terminal Me ester in place of the boronic acid was synthesized, binding measured, and the three-dimensional structure in complex with human thrombin determined by x-ray crystallog. Incubation of Ac-D-Phe-Pro-Arg-OMe, Boc-D-Phe-Pro-Arg-OMe, and H-D-Phe-Pro-Arg-OMe resulted in the formation of thrombin-product complexes within the crystal. Ki values for the corresponding products (free carboxylic acids) were 60±12 μM, 7.8±0.1 μM, 0.58±0.02 μM, resp., indicating that the nature of the N-terminal blocking group has a significant effect on affinity. Examination of the crystal structures indicated that the higher affinity of the H-D-Phe peptide is due to rearrangement of one residue comprising the S3 site (Glu192) to maximize electrostatic interactions with the "NH3+-" of H-D-Phe. The relative affinity of Boc-D-Phe-Pro-Arg-OH is due to favorable hydrophobic interactions between thrombin and the bulky Bu

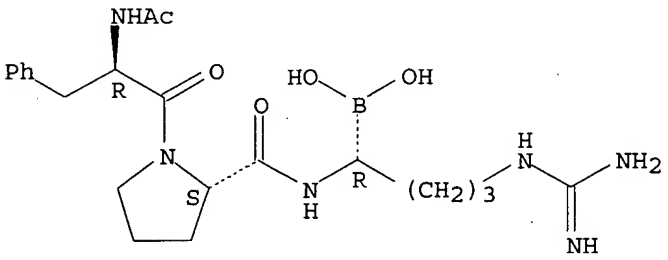
group. However, this results in less favorable binding of Arg-P1 in the oxyanion hole as shown by long hydrogen-bonding distances. This work gave rise to some general observations applicable to structure-based drug design: (1) altering the structure of an inhibitor at one site can affect binding at an unchanged distal site; (2) minor alteration of inhibitor structure can lead to small, but significant reorganization of neighboring protein structure, and these unexpected reorganizations can define alternate binding motifs.

IT **130982-43-3**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(complexes with thrombin; structure-based understanding of ligand affinity using human thrombin as model system)

RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 27 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:339247 HCAPLUS

DOCUMENT NUMBER: 125:48794

TITLE: Flow cytometric evaluation of the effect of various thrombin inhibitors on platelet activation in whole blood

AUTHOR(S): Kaiser, Brigitte; Koza, Michael; Walenga, Jeanine M.; Fareed, Jawed

CORPORATE SOURCE: Cent. Vascular Biol. Med., Friedrich Schiller Univ. Jena, Erfurt, D-99089, Germany

SOURCE: Thrombosis Research (1996), 82(3), 257-263
CODEN: THBRAA; ISSN: 0049-3848

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In an in vitro study, the effect of various thrombin inhibitors (argatroban, efegatran, DuP 714, recombinant hirudin and PEG-hirudin) on platelet activation in whole blood was investigated. Blood was drawn from normal human volunteers using the double syringe technique without use of a tourniquet to avoid auto-aggregation of platelets. Blood was anticoagulated with either argatroban, efegatran, DuP 714, hirudin or PEG-hirudin at final concns. of 10 μg/mL. Blood samples were then incubated at 37°C either with saline, r-tissue factor, arachidonic acid, ADP or collagen. At definite times (1, 2.5, 5, 10 min) aliquots were taken and after various steps of fixative procedure the percentage of platelet activation was measured using fluorescent monoclonal antibodies to platelet surface receptors GPIIIa (CD-61) and P-selectin (CD-62). Flow cytometric anal. showed a platelet activation after all agonists used.

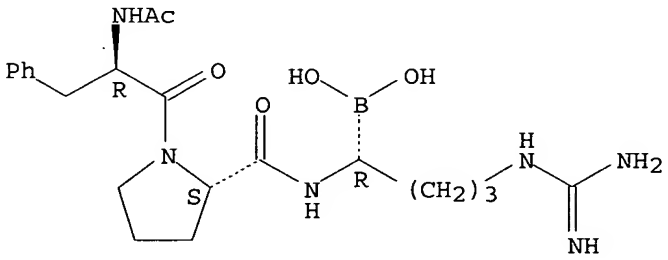
All thrombin inhibitors studied caused a nearly complete inhibition of r-tissue factor-mediated platelet activation. In contrast, after activation with the other agonists an increased percent CD-62 expression was found with a maximum after 2.5 to 5 min. The results show that in whole blood thrombin inhibitors are effective in preventing platelet activation induced by r-tissue factor. The formation of active serine proteases including thrombin may be effectively inhibited by these agents. The observations further suggest that while thrombin inhibitors may control serine proteases, these agents do not inhibit the activation of platelets mediated by other agonists.

IT **130982-43-3**, DuP 714
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flow cytometric evaluation of various thrombin inhibitors effect on platelet activation in whole blood)

RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 28 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:238341 HCAPLUS

DOCUMENT NUMBER: 124:336443

TITLE: Heparin enhances the catalytic activity of des-ETW-thrombin

AUTHOR(S): Goodwin, Christopher A.; Deadman, John J.; Le Bonniec, Bernard F.; Elgendy, Said; Kakkar, Vijay V.; Scully, Michael F.

CORPORATE SOURCE: Thrombosis Res. Inst., London, SW3 6LR, UK

SOURCE: Biochemical Journal (1996), 315(1), 77-83
CODEN: BIJOAK; ISSN: 0264-6021

PUBLISHER: Portland Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The thrombin mutant, des-ETW-thrombin, lacking Glu146, Thr147, and Trp148 within a unique insertion loop located at the extreme end of the primary specificity pocket, has been shown previously to exhibit reduced catalytic activity with respect to macromol. and synthetic thrombin substrates and reduced or enhanced susceptibility to inhibition. Investigation of the hydrolysis of peptidyl p-nitroanilide substrates by des-ETW-thrombin showed increased activity in the presence of heparin and other sulfated glycosaminoglycans. No effect was observed upon the activity of wild-type thrombin. Heparin was found to decrease the Km for cleavage of four thrombin-specific substrates by des-ETW-thrombin, by 3-4-fold. Similarly, pentosan polysulfate (PPS) decreased the Km with these substrates by

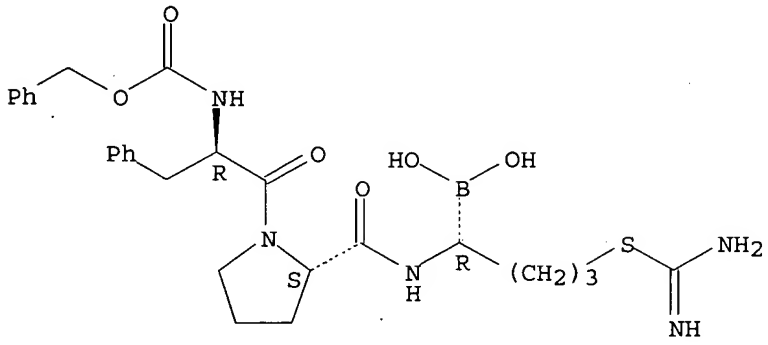
8-10-fold. Heparin also increased the rate of inhibition of des-ETW-thrombin by antithrombin III and D-phenylalanyl-prolyl-arginylchloromethane (PPACK). The inhibition of des-ETW-thrombin by a number of thrombin-specific peptide boronic acids also showed significant reduction in the off-rate. A peptide analog of a sequence of hirudin which binds thrombin tightly to exosite 1 (fibrinogen recognition site) potentiated the activity of des-ETW-thrombin against peptide p-nitroanilide substrates in a manner similar to heparin. The Ki for the inhibition of des-ETW-thrombin by p-aminobenzamidine was decreased by these ligands from 9.7 mM to 7.5 mM, 5.1 mM and 2.5 mM in the presence of heparin, hirudin peptide and PPS resp., suggesting the increased catalytic is due to enhanced access to the primary specificity pocket. The pos. influence of these ligands on des-ETW-thrombin was reversed in the presence of ATP or ADP; the latter has previously been shown to inhibit thrombin activity by blocking initial interaction with fibrinogen at exosite 1. Because the effect of heparin and PPS is similar to that of hirudin peptide, it is proposed that the most likely mechanism is that binding at the heparin-binding site (thrombin exosite 2) facilitated interaction at exosite 1 causing a conformational change which partially corrects the defective ground-state binding of the mutant thrombin. Although no effect was observed upon the activity of wild-type thrombin, our findings do provide further evidence of an allosteric property of thrombin which may control the geometry of, and access to, the primary specificity pocket.

IT **176701-90-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(heparin enhances the catalytic activity of des-ETW-thrombin)

RN 176701-90-9 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)thio]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 29 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:110136 HCAPLUS

DOCUMENT NUMBER: 124:261704

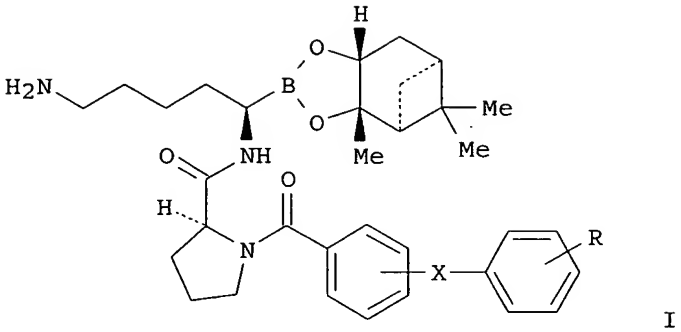
TITLE: Synthesis of conformationally restricted boropeptide thrombin inhibitors

AUTHOR(S): Cacciola, Joseph; Fevig, John M.; Alexander, Richard S.; Brittelli, David R.; Kettner, Charles A.; Knabb, Robert M.; Weber, Patricia C.

CORPORATE SOURCE: DuPont Merck Pharm. Co., Wilmington, DE, 19880-0500, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (1996), 6(3),

301-6
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



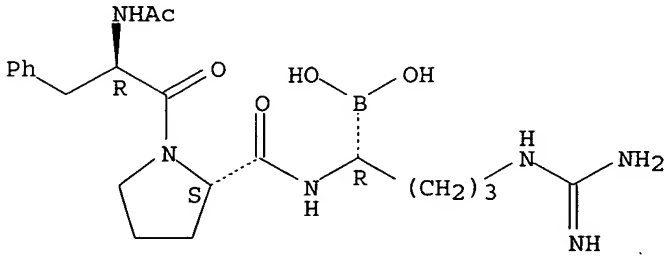
I

AB A series of boropeptide thrombin inhibitors I.HCl (X = o-CH2, m-CH2, p-CH2, o-O, m-O, m-CH2, m-S, m-SO2; R = H, 2-CF3, 2-Me, 2-SMe, 2-Br, 3-F, 3-CF3, 4-CF3, 3,4-methylenedioxy, 2-OMe, 4-OMe) was prepared in which the P3 residues of borolysine peptides were replaced by conformationally-restricted, benzoic acid-derived residues. The potent binding affinity of the resulting inhibitors such as I (X = m-CH2, R = 2-CF3) may be due in part to a unique mode of binding in the thrombin active site.

IT **130982-43-3DP**, DuP 714, conformationally restricted benzoic acid derivs. **175272-74-9DP**, conformationally restricted benzoic acid derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of conformationally restricted boropeptide thrombin inhibitors)

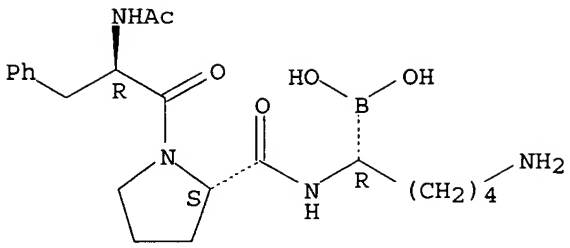
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 175272-74-9 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-(5-amino-1-boronopentyl)-, monohydrochloride, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

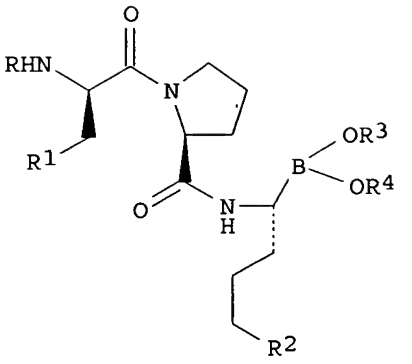


● HCl

L13 ANSWER 30 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:994800 HCAPLUS
DOCUMENT NUMBER: 124:117999
TITLE: Preparation of boronic peptides as antithrombotics
INVENTOR(S): Mallart, Sergio; Lassalle, Gilbert; Purcell, Thomas Andrew; Muller, Jean Claude
PATENT ASSIGNEE(S): Synthelabo S. A., Fr.
SOURCE: Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 677531	A1	19951018	EP 1995-400776	19950407
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
FR 2718451	A1	19951013	FR 1994-4288	19940412
FR 2718451	B1	19960510		
CA 2146833	AA	19951013	CA 1995-2146833	19950411
FI 9501726	A	19951013	FI 1995-1726	19950411
NO 9501418	A	19951013	NO 1995-1418	19950411
AU 9516380	A1	19951019	AU 1995-16380	19950411
JP 07285990	A2	19951031	JP 1995-85270	19950411
CN 1113493	A	19951220	CN 1995-103889	19950411
ZA 9502983	A	19960111	ZA 1995-2983	19950411
HU 71617	A2	19960129	HU 1995-1041	19950411

PRIORITY APPLN. INFO.: FR 1994-4288 A 19940412
OTHER SOURCE(S): MARPAT 124:117999
GI



I

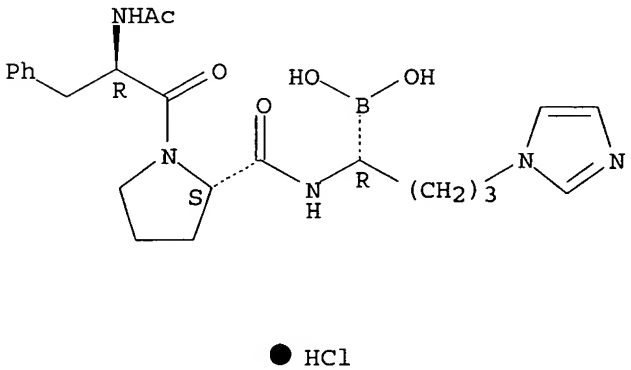
AB Boronic peptides I [R = H, alkyl, acyl, carboxylate; R1 = Ph, cyclohexyl; R2 = (un)substituted imidazole; R3,R4 = H, alkoxy] were prepared as antithrombotics. Thus, I (R = Ac, R1 = Ph, R2 = imidazolyl, R3 = R4 = H) was prepared and tested for its antithrombotic activity (no data).

IT **172831-94-6P 172831-96-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of boronic peptides as antithrombotics)

RN 172831-94-6 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-(1H-imidazol-1-yl)butyl]-, monohydrochloride, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

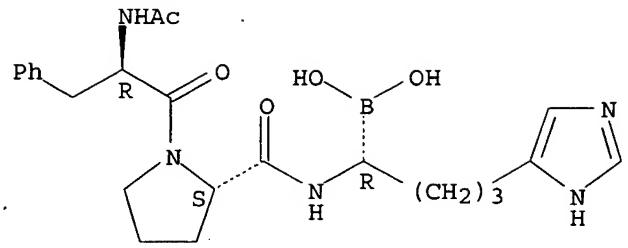


● HCl

RN 172831-96-8 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-(1H-imidazol-4-yl)butyl]-, monohydrochloride, (R)- (9CI) (CA INDEX NAME)

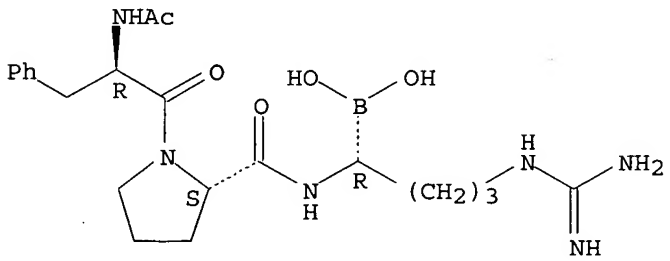
Absolute stereochemistry.



● HCl

L13 ANSWER 31 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:777429 HCAPLUS
DOCUMENT NUMBER: 123:275182
TITLE: New tripeptidic thrombin inhibitors. Influence of P2 and P3 residues on activity and selectivity
AUTHOR(S): De Nanteuil, Guillaume; Gloanec, Philippe; Lila, Christine; Portevin, Bernard; Boudon, Alain; Rupin, Alain; Verbeuren, Tony J.
CORPORATE SOURCE: Div. Medicinal Chem., Inst. Recherche Servier, Suresnes, 92150, Fr.
SOURCE: Bioorganic & Medicinal Chemistry (1995), 3(8), 1019-24
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Structural variations of P2 and P3 residues in tripeptidic boroarginine thrombin inhibitors led to compds. with similar potency than reference compound DuP 714, but with enhanced selectivity for thrombin compared to plasmin.
IT **130982-43-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(new tripeptidic boroarginine thrombin inhibitors and influence of P2 and P3 residues on activity and selectivity in relation to plasmin)
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 32 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:763508 HCAPLUS
DOCUMENT NUMBER: 123:199406
TITLE: Preparation of amidino- and guanidino-substituted (peptidyl)boronic acid inhibitors of trypsin-like enzymes.
INVENTOR(S): Fevig, John Matthew; Kettner, Charles Adrian; Lee, Sheng-Lian O.; Carini, David John
PATENT ASSIGNEE(S): Du Pont Merck Pharmaceutical Co., USA
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9425049	A1	19941110	WO 1994-US4058	19940421
W: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, SK				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2161216	AA	19941110	CA 1994-2161216	19940421
AU 9467038	A1	19941121	AU 1994-67038	19940421
EP 696199	A1	19960214	EP 1994-914776	19940421
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08509723	T2	19961015	JP 1994-524316	19940421
ZA 9402899	A	19951026	ZA 1994-2899	19940426

PRIORITY APPLN. INFO.:
US 1993-52835 A 19930427
US 1994-204055 A 19940302
WO 1994-US4058 W 19940421

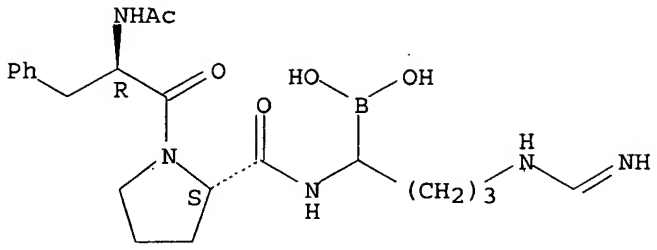
OTHER SOURCE(S): MARPAT 123:199406

AB R3AnNR2CHR1BY1Y2 [R1 = alkyl substituted with cyano, NHCH(:NH), NHC(:NH)NHOH, etc., substituted phenyl(alkyl); R2 = H, alkyl, (substituted) Ph, naphthyl; R3 = H, alkyl, aryl, alkylaryl, blocking group; A = amino acid residue or peptide residue containing 2-20 amino acid residues; Y1, Y2 = OH, F, alkoxy; Y1Y2 = cyclic boron ester; n = 0, 1], were prepared Thus, BOC-D-Phe-Pro-NHCH[(CH2)3NHCH(:NH)]B(OH)2 (solution phase preparation given) inhibited thrombin with Ki = 0.040 nM.

IT **167088-06-4P 167088-15-5P 167088-16-6P**
167088-24-6P 167088-25-7P 167088-26-8P
167088-27-9P 167088-41-7P 167088-42-8P
167088-44-0P 167088-45-1P 167088-49-5P
167088-50-8P 167088-51-9P 167088-52-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amidino and guanidino substituted peptidylboronic acid inhibitors of trypsin-like enzymes)

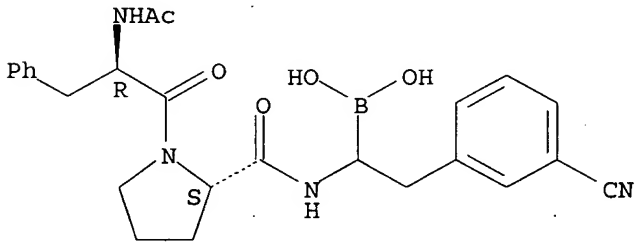
RN 167088-06-4 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



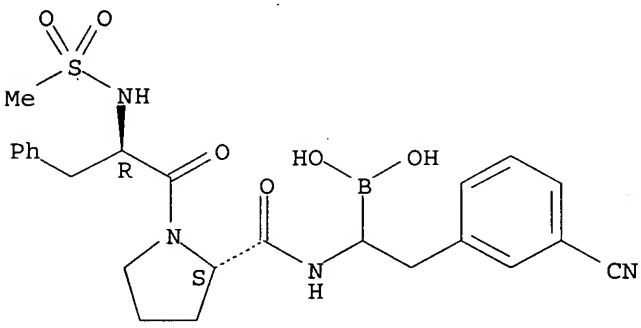
RN 167088-15-5 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-2-(3-cyanophenyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



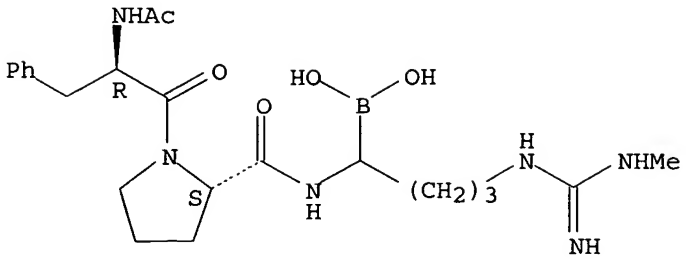
RN 167088-16-6 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[1-borono-2-(3-cyanophenyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 167088-24-6 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

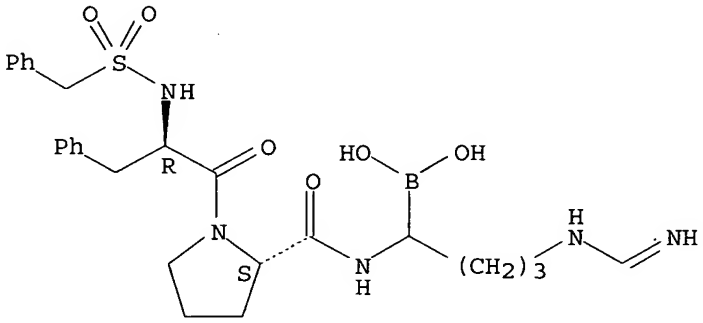
Absolute stereochemistry.



● HCl

RN 167088-25-7 HCAPLUS
CN L-Prolinamide, N-[(phenylmethyl)sulfonyl]-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

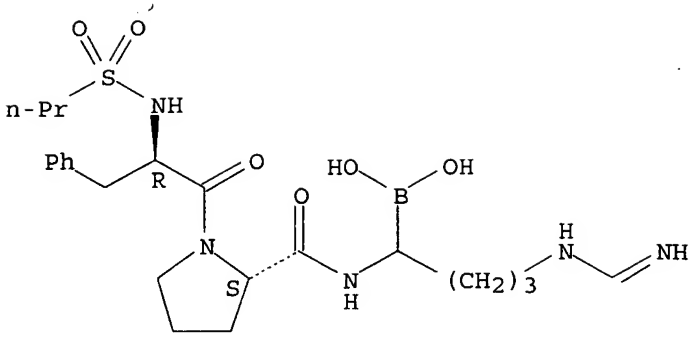
Absolute stereochemistry.



● HCl

RN 167088-26-8 HCAPLUS
CN L-Prolinamide, N-(propylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

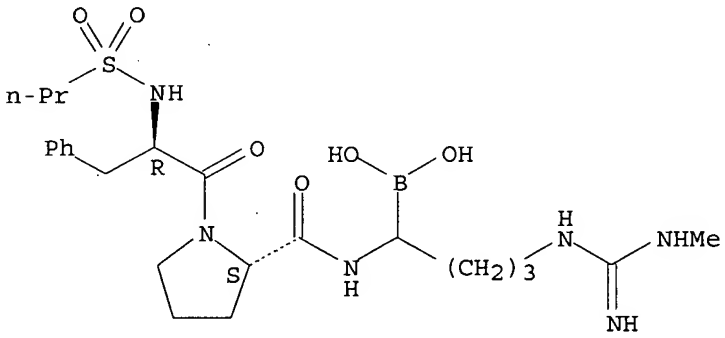
Absolute stereochemistry.



● HCl

RN 167088-27-9 HCAPLUS
CN L-Prolinamide, N-(propylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

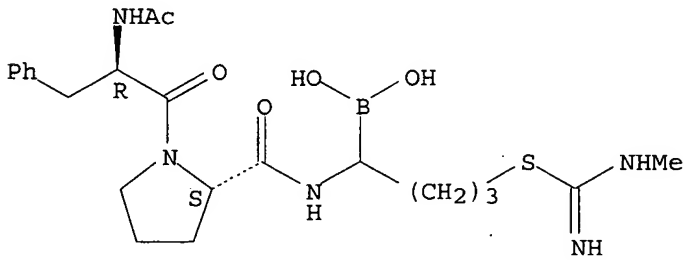
Absolute stereochemistry.



● HCl

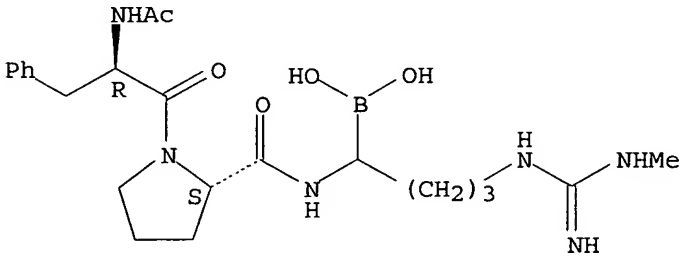
RN 167088-41-7 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]thio]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



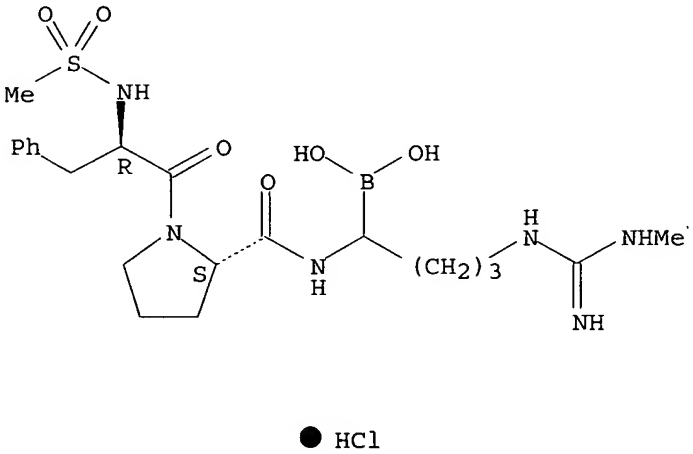
RN 167088-42-8 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



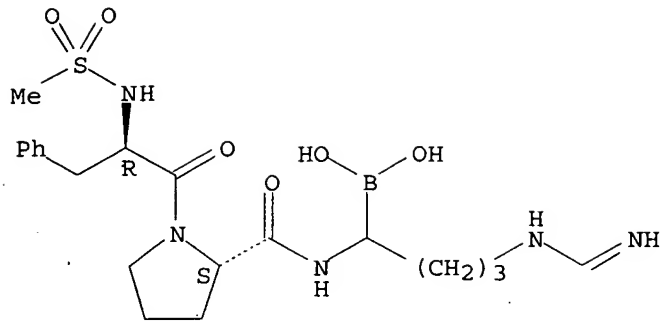
RN 167088-44-0 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 167088-45-1 HCAPLUS
CN L-Prolinamide, N-(methylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

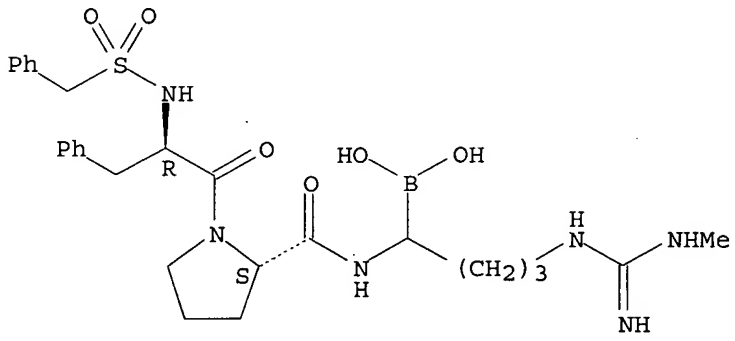
Absolute stereochemistry.



● HCl

RN 167088-49-5 HCAPLUS
CN L-Prolinamide, N-[(phenylmethyl)sulfonyl]-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

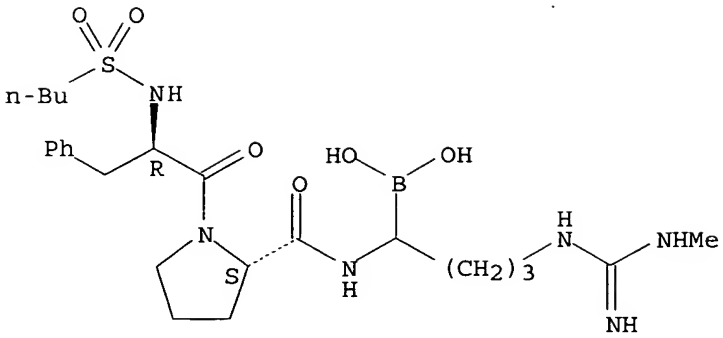
Absolute stereochemistry.



● HCl

RN 167088-50-8 HCAPLUS
CN L-Prolinamide, N-(butylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[[imino(methylamino)methyl]amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

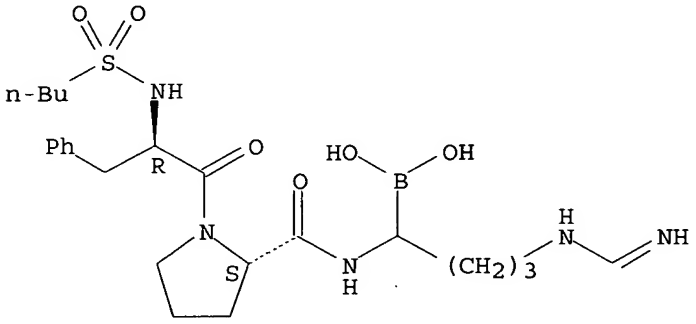
Absolute stereochemistry.



● HCl

RN 167088-51-9 HCAPLUS
CN L-Prolinamide, N-(butylsulfonyl)-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

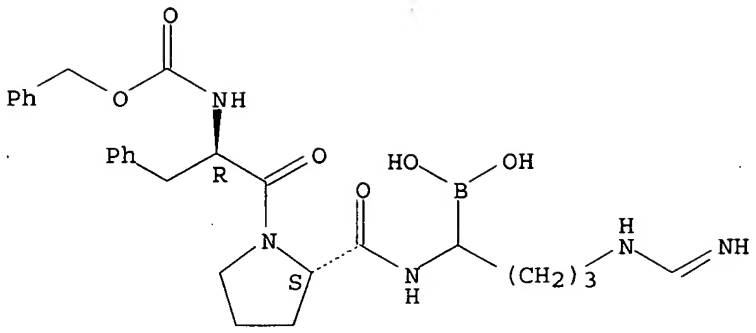
Absolute stereochemistry.



● HCl

RN 167088-52-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[1-borono-4-[(iminomethyl)amino]butyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L13 ANSWER 33 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:761808 HCAPLUS
DOCUMENT NUMBER: 123:164691
TITLE: Blood coagulation retardants and devices
INVENTOR(S): Lyon, Martha E.; Henderson, Paul; Malik, Sohail; Kenny, Margaret A.; Lyon, Andrew W.
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

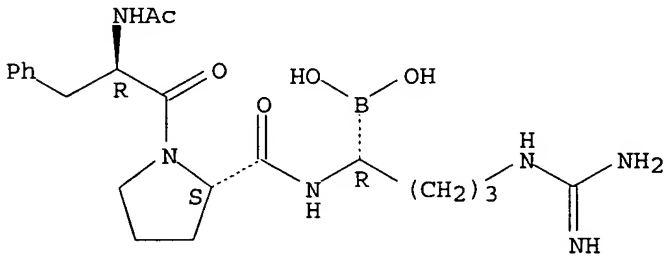
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9514788	A1	19950601	WO 1994-US13537	19941123
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9511862	A1	19950613	AU 1995-11862	19941123
PRIORITY APPLN. INFO.:			US 1993-157880 A	19931124
			WO 1994-US13537 W	19941123

AB The invention provides methods of using anticoagulants to retard the coagulation of blood, so that properties and functions of blood, plasma, and blood cells may be determined anal. The methods do not interfere with electrochem. techniques use to detect divalent cations and permit accurate anal. of many analytes within a single blood sample, which currently require sep. anticoagulated blood samples. The serine protease inhibitors used may be combined with each other or blood cell activation, aggregation, and adhesion inhibitors in mixts. that provide anticoagulant activity. The methods permit, for the first time, the possibility of using a single blood sample to perform a full range of blood, plasma, and blood cell analyses. The anticoagulation effect of D-phenylalanyl-prolyl-arginyl chloromethyl ketone is determined

IT **130982-43-3**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(blood coagulation retardants and devices)
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 34 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:723126 HCAPLUS
DOCUMENT NUMBER: 123:144640
TITLE: Removal of boronic acid protecting groups from boropeptides by transesterification.
INVENTOR(S): Kettner, Charles Adrian
PATENT ASSIGNEE(S): Du Pont Merck Pharmaceutical Co., USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9421668	A1	19940929	WO 1994-US2964	19940323
W: AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5384410	A	19950124	US 1993-36378	19930324
AU 9464486	A1	19941011	AU 1994-64486	19940323
PRIORITY APPLN. INFO.:			US 1993-36378 A	19930324
			WO 1994-US2964 W	19940323

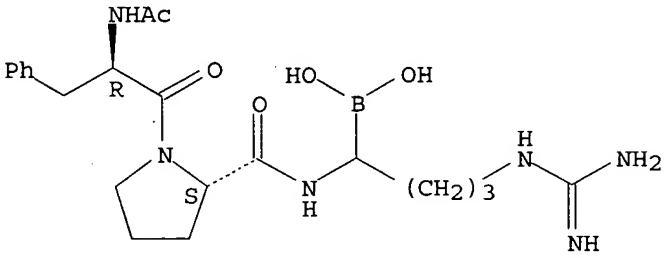
OTHER SOURCE(S): CASREACT 123:144640; MARPAT 123:144640
GI For diagram(s), see printed CA Issue.
AB R1XnNHCH(R2)B(OH)2 [R1 = H, protecting group, Ar(CH2)mSO2; Ar = substituted Ph, naphthyl, biphenyl; X = peptide of 1-20 amino acids; R2 = (substituted) alkyl, Ar(CH2)n; m = 0-2; n = 0, 1], were prepared by suspending R1XnNHCH(R2)BR3R4 (R3, R4 = alkoxy; R3R4 = atoms to form a cyclic boronic ester optionally containing a heteroatom) in a mixture of H2O and a H2O-immiscible organic solvent containing ≥1 equivalent of an organic boronic acid, stirring the mixture for ≈1h, allowing the mixture to sep. into 2 phases, separating the phases, and recovering product from the aqueous phase.

Thus, 100 mg boropeptide pinacol ester I (MeOSuc = MeO2CCH2CH2CO) was stirred with 5 equivalent PhB(OH)2 in H2O/Et2O to give 92 mg deprotected boropeptide containing <10% I.

IT **124215-57-2P 165946-14-5P 166239-18-5P 166239-20-9P 166239-21-0P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(removal of boronic acid protecting groups from boropeptides by transesterification)

RN 124215-57-2 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-boronobutyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



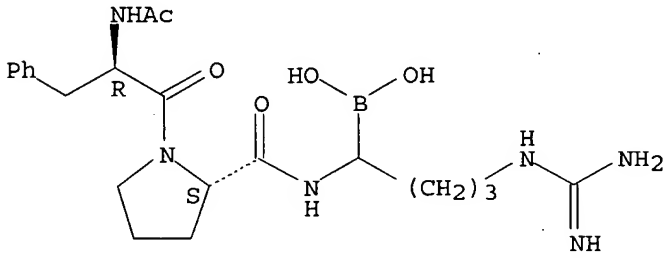
● HCl

RN 165946-14-5 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-boronobutyl]-, monobenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

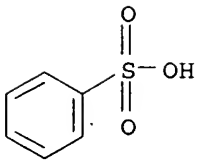
CRN 124216-70-2
CMF C21 H33 B N6 O5

Absolute stereochemistry.



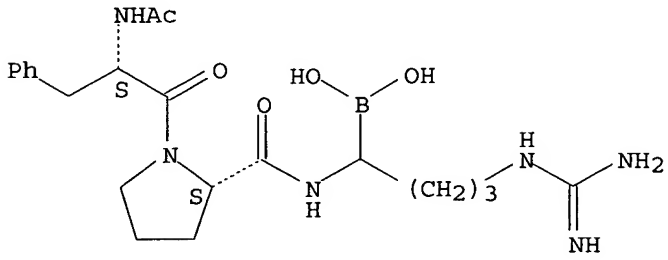
CM 2

CRN 98-11-3
CMF C6 H6 O3 S



RN 166239-18-5 HCAPLUS
CN L-Prolinamide, N-acetyl-L-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-boronobutyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



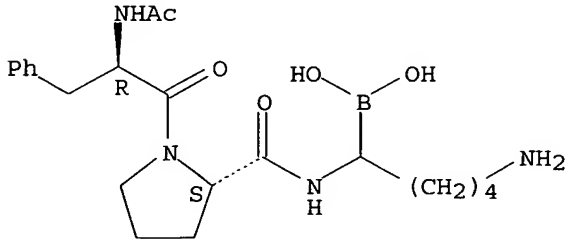
● HCl

RN 166239-20-9 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-(5-amino-1-boronopentyl)-, monobenzenesulfonate (9CI) (CA INDEX NAME)

CM 1

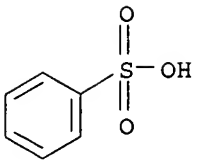
CRN 166239-19-6
CMF C21 H33 B N4 O5

Absolute stereochemistry.



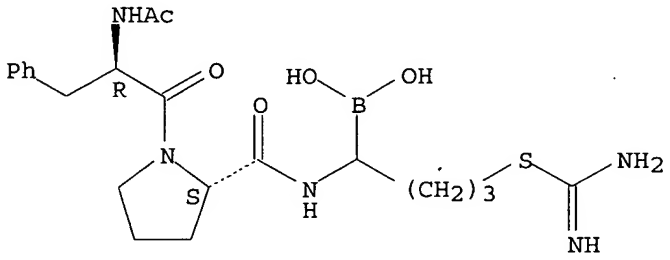
CM 2

CRN 98-11-3
CMF C6 H6 O3 S



RN 166239-21-0 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[4-[(aminoiminomethyl)thio]-1-boronobutyl]-, monohydrobromide (9CI) (CA INDEX NAME)

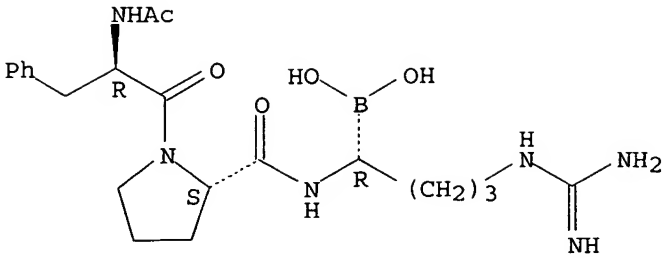
Absolute stereochemistry.



● HBr

L13 ANSWER 35 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:591883 HCAPLUS
DOCUMENT NUMBER: 123:286689
TITLE: Synthesis of Thrombin Inhibitor DuP 714
AUTHOR(S): Wityak, John; Earl, Richard A.; Abelman, Matthew M.; Bethel, Yvonne B.; Fisher, Barbara N.; Kauffman, Goss S.; Kettner, Charles A.; Ma, Philip; McMillan, Janice L.; et al.
CORPORATE SOURCE: Du Pont Merck Pharmaceutical Company, Wilmington, DE, 19880-0402, USA
SOURCE: Journal of Organic Chemistry (1995), 60(12), 3717-22
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 123:286689
AB The asym. synthesis of thrombin inhibitor DuP 714 is described. The route uses the Matteson boronic ester homologation to prepare a key intermediate α-aminoboronic acid. New methodol. was developed for the formamidination of boroornithine peptides and for pinanediol boronate ester cleavage.
IT **131062-98-1P**, Dup 714 hydrochloride
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of thrombin inhibitor DuP 714)
RN 131062-98-1 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

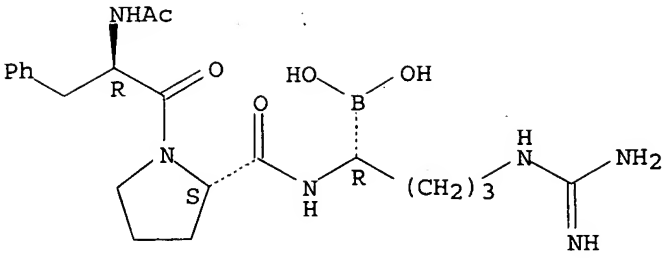
L13 ANSWER 36 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:585169 HCAPLUS
DOCUMENT NUMBER: 123:624
TITLE: Direct inhibition of protein Ca by site directed thrombin inhibitors: implications in anticoagulant and thrombolytic therapy
AUTHOR(S): Callas, Demetra D.; Fareed, Jawed
CORPORATE SOURCE: Departments of Pharmacology and Pathology, Loyola Univ. Chicago, Stritch School of Medicine, Maywood, IL, 60153, USA
SOURCE: Thrombosis Research (1995), 78(5), 457-60
CODEN: THBRAA; ISSN: 0049-3848
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The current studies were designed to investigate the direct inhibitory effects of synthetic and recombinant antithrombin agents on the amidolytic action of protein Ca. Of the thrombin inhibitors tested, Ac-D-Phe-Pro-boroArg-OH was the most potent inhibitor, followed closely by D-Phe-Pro-Arg-H, D-MePhe-Pro-Arg-H and Boc-D-Phe-Pro-Arg-H. Aprotinin had a similar anti-protein Ca activity, whereas Argatroban, Hirulog-1, hirudin, and heparin did not produce an inhibition greater than 25%. The levels of these agents that inhibit protein Ca are higher than those used in antithrombotic therapy, but equivalent to those used for thrombolytic therapy.

IT **130982-43-3**, DuP 714
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(direct inhibition of protein Ca by site directed thrombin inhibitors in relation to anticoagulant and thrombolytic therapy)

RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 37 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:413502 HCAPLUS
DOCUMENT NUMBER: 122:259717
TITLE: Kinetic and Crystallographic Studies of Thrombin with Ac-(D)Phe-Pro-boroArg-OH and Its Lysine, Amidine, Homolysine, and Ornithine Analogs
AUTHOR(S): Weber, Patricia C.; Lee, Sheng-Lian; Lewandowski, Francis A.; Schadt, Margaret C.; Chang, Chong-Hwan; Kettner, Charles A.
CORPORATE SOURCE: Chemical and Physical Sciences Department, The Du Pont Merck Pharmaceutical Company, Wilmington, DE, 19880-0228, USA
SOURCE: Biochemistry (1995), 34(11), 3750-7
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

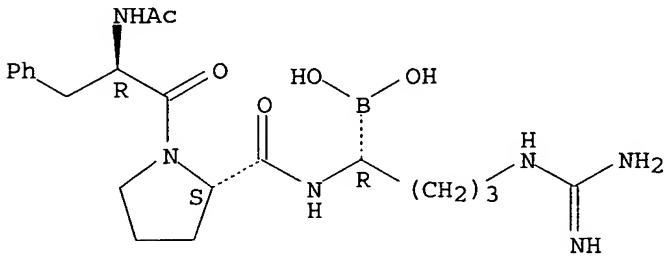
AB The x-ray crystallog. structure of Ac-(D)Phe-Pro-boroArg-OH (DuP714, Ki = 0.04 nM) complexed with human α-thrombin shows the boron atom covalently bonded to the side-chain oxygen of the active site serine, Ser195. The boron adopts a nearly tetrahedral geometry, and the boronic acid forms a set of interactions with the protein that mimic the tetrahedral transition state of serine proteases. Contributions of the arginine side chain to inhibitor affinity were examined by synthesis of the ornithine, lysine, homolysine, and amidine analogs of DuP714. The basic groups interact with backbone carbonyl groups, water mols., and an aspartic acid side chain (Asp189) located in the thrombin S1 specificity pocket. The variation in inhibition constant by 3 orders of magnitude appears to reflect differences in the energetics of interactions made with thrombin and differences in ligand flexibility in solution Kinetic and crystallog. data are reported for the following thrombin inhibitors: DuP714 (space group C2, a = 70.8 Å, b = 72.3 Å, c = 72.6 Å, β = 100.6°, crystallog. R-factor = 0.204 to 1.95 Å resolution); Ac-(D)Phe-Pro-boroLys-OH (Ki = 0.24 nM, C2, a = 70.3 Å, b = 71.9 Å, c = 71.9 Å, β = 100.9°, R-factor = 0.201 to 2.35 Å resolution); Ac-(D)Phe-Pro-boro-homoLys-OH (Ki = 8.1 nM, C2, a = 70.3 Å, b = 71.9 Å, c = 71.9 Å, β = 100.9°, R-factor = 0.212 to 2.4 Å resolution); Ac-(D)Phe-Pro-boroOrn-OH (Ki = 79 nM, C2, a = 70.4 Å, b = 72.2 Å, c = 72.2 Å, β = 100.1°, R-factor = 0.195 to 2.25 Å resolution); and Ac-(D)Phe-Pro-boro-n-butylamidinoGly-OH (Ki = 0.29 nM, C2, a = 70.8 Å, b = 72.4 Å, c = 72.2 Å, β = 100.3°, R-factor = 0.197 to 2.25 Å resolution).

IT **130982-43-3P**, DuP 714 **162518-90-3P 162518-91-4P 162518-92-5P 162518-93-6P**
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC

(Process)
(kinetic and crystallog. studies of thrombin with Ac-(D)Phe-pro-boroArg-OH and lysine and amidine and homolysine and ornithine analogs)

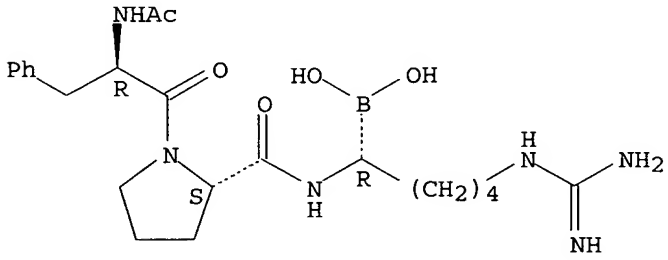
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



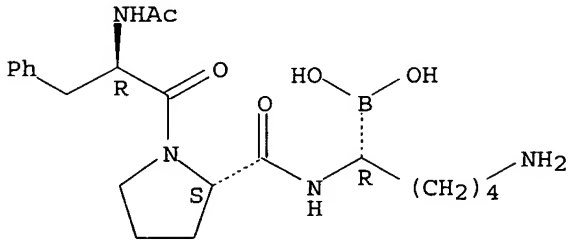
RN 162518-90-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[5-[(aminoiminomethyl)amino]-1-boronopentyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



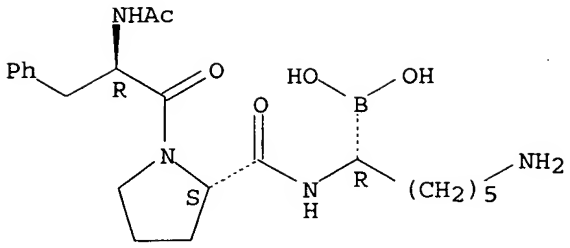
RN 162518-91-4 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-(5-amino-1-boronopentyl)-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



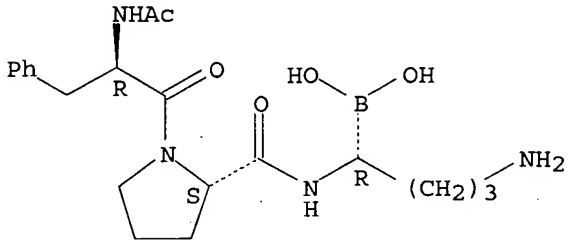
RN 162518-92-5 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-(6-amino-1-boronohexyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 162518-93-6 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-(4-amino-1-boronobutyl)-, (R)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 38 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:389760 HCAPLUS
DOCUMENT NUMBER: 122:151379
TITLE: Fibrin-binding antibody-thrombin inhibitor chimeric molecules and their use as antithrombotics
INVENTOR(S): Haber, Edgar; Bode, Christoph; Runge, Marschall S.
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA; Emory University
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9425491	A1	19941110	WO 1994-US4881	19940503
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5443827	A	19950822	US 1993-58699	19930503
CA 2161772	AA	19941110	CA 1994-2161772	19940503
EP 713496	A1	19960529	EP 1994-915992	19940503
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08509618	T2	19961015	JP 1994-524639	19940503
PRIORITY APPLN. INFO.:			US 1993-58699 A	19930503
			WO 1994-US4881 W	19940503

AB A chimeric mol. that contains a fibrin-binding portion of an antibody covalently linked to an inhibitor of thrombin, which mol. may be

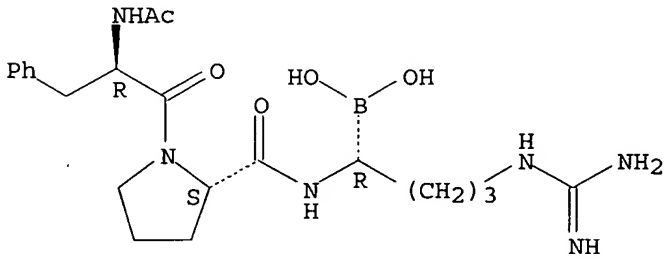
administered to inhibit thrombus formation and growth, is claimed. Anti-fibrin monoclonal IgG 59D8 or its Fab' fragment was chemical conjugated to hirudin. In tests of inhibition of thrombus growth in human plasma, the conjugate was 10-fold more potent that hirudin alone.

IT **130982-43-3D**, conjugates with anti-fibrin antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fibrin-binding antibody-thrombin inhibitor chimeric mols. and their use as antithrombotics)

RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 39 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1995:269563 HCAPLUS

DOCUMENT NUMBER: 122:127899

TITLE: Improved sensitivity by online isotachophoretic preconcentration in the capillary zone electrophoretic determination of peptide-like solutes

AUTHOR(S): Witte, Dirk T.; Nagard, Sofia; Larsson, Marita

CORPORATE SOURCE: Department of Bioanalytical Chemistry, Astra Haessle AB, Molndal, S-431 83, Swed.

SOURCE: Journal of Chromatography, A (1994), 687(1), 155-66
CODEN: JCRAEY; ISSN: 0021-9673

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

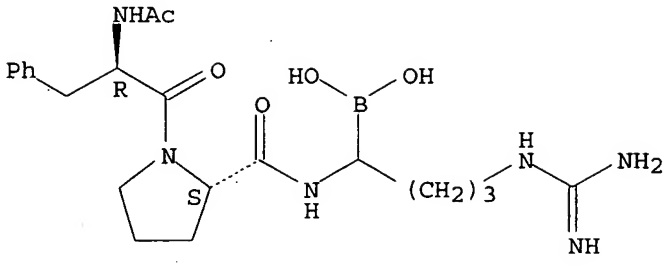
AB Isotachophoresis (ITP) was studied as an online preconcn. technique in combination with capillary zone electrophoresis for the determination of pos. charged peptide-like solutes. This paper shows the effects of different electrolyte compns., different ITP times and various injection vols. on the time necessary for stacking and destacking. Injection vols. as large as 1.4 μL resulted in a resolution between the test peptides similar to that of pure capillary zone electrophoresis. Calibration graphs were linear in a range from 15 μmol/L down to 30 nmol/L after injections of 1.4 μL. Initial studies of plasma exts. appeared promising, although in the long term the overall efficiency decreased.

IT **124216-70-2**
RL: ANT (Analyte); ANST (Analytical study)
(online isotachophoretic preconcn. in capillary zone electrophoresis of peptide-like solutes)

RN 124216-70-2 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 40 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:692370 HCAPLUS
DOCUMENT NUMBER: 121:292370
TITLE: Thrombin inhibitors and anti-coagulants on thrombin-induced embolization in rabbit cranial vasculature
AUTHOR(S): Liu, Jun T.; Paul, William; Emerson, Michael; Cicala, Carla; Page, Clive P.
CORPORATE SOURCE: Department of Pharmacology, King's College, University of London, Manresa Road, London, SW3 6LX, UK
SOURCE: European Journal of Pharmacology (1994), 264(2), 183-90
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

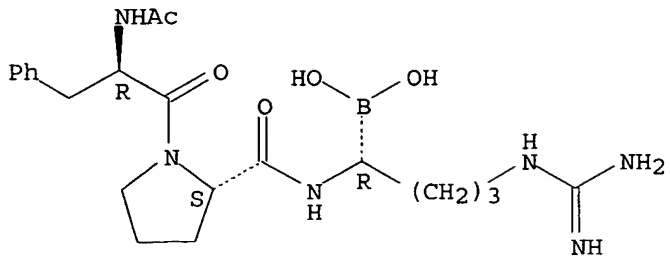
AB 111Indium-labeled platelets were continuously monitored in the cranial vasculature of anesthetized rabbits and thrombin inhibitors and anti-coagulants were tested on the sustained platelet accumulation induced by intracarotid injection of thrombin (90 U/kg). Pretreatment, commencing 30 min prior to thrombin, with a 1-h intracarotid infusion of D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone (PPACK; 0.25-1.0 μg/kg per min), unfractionated heparin (Multiparin; 5-20 U/kg bolus+0.75-3.0 U/kg per min infusion) or low mol. weight heparin (Fragmin; 2.4-9.6 U/kg per min) produced dose-related redns. in platelet accumulation. Continuous infusion of acetyl-D-phenylalanyl-prolyl-boroarginine (DuP-714 ester; 30 μg/kg per min) for 30 min induced marked accumulation of platelets in the pulmonary circulation in the absence of thrombin. Bolus intracarotid injection, 1 min before thrombin, of Hirulog (0.05-0.2 mg/kg), PPACK (10-30 μg/kg), Multiparin (25-100 U/kg), Fragmin (150 U/kg) or DuP-714 ester (15-30 μg/kg) caused significant redns. in platelet accumulation. When injected 1 min after thrombin, Hirulog (1 mg/kg), PPACK (100 μg/kg), Fragmin (150 U/kg) and DuP-714 ester (30 μg/kg) had no significant effect and Multiparin (100 U/kg) increased platelet accumulation. The results demonstrate that pretreatment with a range of thrombin inactivators, acting via different mechanisms, can inhibit thrombin-induced cerebral thromboembolism in the rabbit.

IT **130982-43-3**, DuP-714
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thrombin inhibitors and anticoagulants inhibition of thrombin-induced cerebral platelet accumulation)

RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-

1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

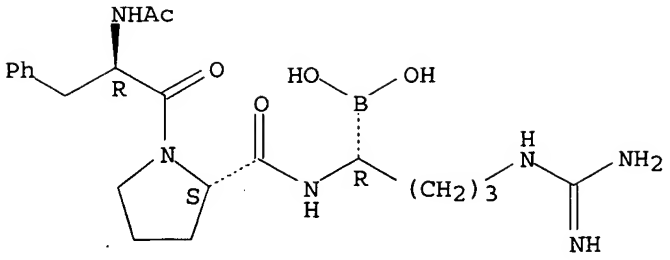


L13 ANSWER 41 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:671152 HCAPLUS
DOCUMENT NUMBER: 121:271152
TITLE: analysis of the thrombin inhibitor DuP 714 by an enzyme-linked immunosorbent assay
AUTHOR(S): Mitchell, T. J.; Knabb, R. M.; Christ, D. D.; Farmer, A. R.; Reilly, T. M.
CORPORATE SOURCE: DuPont Merck Pharmaceutical Co. Experimental Station, Wilmington, DE, 19880-0400, USA
SOURCE: Blood Coagulation & Fibrinolysis (1994), 5(4), 517-21
CODEN: BLFIE7; ISSN: 0957-5235
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A competition ELISA has been developed for the quant. detection in plasma of DuP 714, a boroarginine tripeptide (Ac-(D)-Phe-Pro-boroArg) with potent antithrombin activity. The assay has been used to calculate the half-life after i.v. administration of DuP 714, as well as the percent bioavailability after oral administration of the agent. Following i.v. administration, in dogs, the clearance of compound from the circulation could best be fit to a biexponential decay with an initial half-life of approx. 9 min, and a slower elimination phase with a half-life of 40 min. There was a significant correlation between pharmacokinetic and pharmacodynamic characteristics ($r = 0.9570$, $P < 0.01$) as measured with the ELISA and the clotting assay, aPTT, following i.v. infusion in conscious dogs. A plasma concentration of 311 ng/mL doubled the aPTT. After oral administration of 1 mg/kg DuP 714, peak concentration ranged from 384 to 584 ng/mL. Oral bioavailability, determined by comparing the areas under concentration vs time curves after oral and i.v. administration, was 53 ± 8% (n = 4). In summary, this assay offers a rapid, sensitive and specific method of examining the peptide's pharmacokinetic characteristics.

IT **130982-43-3**, DuP 714
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(anal. of thrombin inhibitor DuP 714 in blood plasma by ELISA)
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

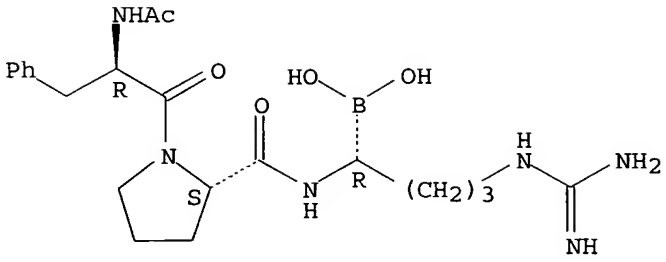


L13 ANSWER 42 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:548612 HCAPLUS
DOCUMENT NUMBER: 121:148612
TITLE: Platelet deposition induced by severely damaged vessel wall is inhibited by a boroarginine synthetic peptide with antithrombin activity
AUTHOR(S): Badimon, J. J.; Weng, D.; Chesebro, J. H.; Fuster, V.; Badimon, L.
CORPORATE SOURCE: Massachusetts Gen. Hosp., Boston, MA, USA
SOURCE: Thrombosis and Haemostasis (1994), 71(4), 511-16
CODEN: THHADQ; ISSN: 0340-6245
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of a synthetic α-aminoboronic acid derivative, DuP 714 (Ac,D-Phe-Pro-Boro-Arg-HCl), on platelet deposition on the severely damaged arterial wall were studied. The study was performed in vivo in a porcine model of arterial thrombosis triggered by a severely damaged vessel wall at blood flow conditions mimicking mildly stenotic and patent vessels. In addition, ex-vivo platelet aggregation activity was evaluated by whole blood impedance aggregometry, using collagen, ADP and thrombin as agonists. The synthetic α-aminoboronic peptide was i.v. administered as a bolus followed by continuous infusion. Ex vivo thrombin-induced whole blood platelet aggregation was totally abolished, while ADP- and collagen-induced whole blood platelet aggregation was not modified. The effects of the synthetic antithrombin on platelet deposition were evaluated in native blood (nonanticoagulated) conditions and in combination with heparin. Under both exptl. conditions, the synthetic peptide inhibited platelet deposition at local flow conditions of both high and low shear rates. The results suggest that specific inhibition of locally generated thrombin might be a good strategy to prevent platelet-dependent arterial thrombus formation independently of the local flow shear rate of the area at risk.

IT **130982-43-3**, DuP 714
RL: BIOL (Biological study)
(antithrombotic and blood platelet aggregation-inhibiting activities of)
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

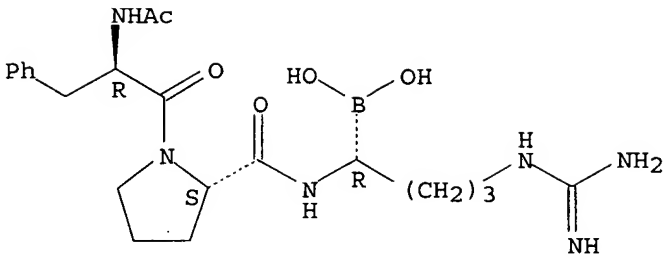


L13 ANSWER 43 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:529186 HCAPLUS
DOCUMENT NUMBER: 121:129186
TITLE: On-column ITP focusing in CZE for the quantitation of low-molecular-weight basic solutes in biological samples
AUTHOR(S): Larsson, Marita; Naagaard, Sofia
CORPORATE SOURCE: Astra Haessle AB, Moelndal, S-431 83, Swed.
SOURCE: Journal of Microcolumn Separations (1994), 6(2), 107-13
CODEN: JMSEEJ; ISSN: 1040-7685
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Capillary zone electrophoretic (CZE) sepns. were performed after the injection of large sample vols. by use of a discontinuous buffer system for analyte focusing. Up to 700 nL were injected into a 75 μm i.d. capillary, corresponding to a 23 cm long sample zone. Automated analyses were performed in a com. available instrument, which was modified to work with a larger pressure drop for hydrodynamic injection. The method was adapted to the determination of a low-mol.-weight enzyme inhibitor, DuP 714, in aqueous samples and a structurally related test compound in exts. from plasma samples. The separation system based on a coated capillary was stable and reproducible over several weeks use for a aqueous samples, containing acetonitrile, indicated that there is a need for more stable coatings or more extensive sample cleanup. Calibration curves are presented for the test substances, showing a linear relationship between the area ratio of the solute vs.an internal standard and the concentration Samples containing 50-100 nmol L-1 of solute could be successfully analyzed by CZE with UV detection at 215 nm, approaching levels that are relevant for bioanal. applications.

IT **130982-43-3**, DuP 714
RL: ANT (Analyte); ANST (Analytical study)
(determination of, by capillary zone electrophoresis, on-column isotachophoresis focusing in)
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 44 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:473892 HCAPLUS
DOCUMENT NUMBER: 121:73892
TITLE: Directing anticoagulants to blood clots using conjugates with ligands for clot proteins and their preparation and use
INVENTOR(S): Eisenberg, Paul; Rylatt, Dennis Brian; Hillyard, Carmel Judith; Bundesen, Peter Gregory
PATENT ASSIGNEE(S): Agen Ltd., Australia
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9409034	A1	19940428	WO 1993-AU524	19931012
W: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9307553	A	19940503	ZA 1993-7553	19931012
AU 9351458	A1	19940509	AU 1993-51458	19931012
EP 668875	A1	19950830	EP 1993-922464	19931012
R: CH, DE, FR, GB, IT, LI				

PRIORITY APPLN. INFO.: AU 1992-5234 A 19921012
WO 1993-AU524 W 19931012

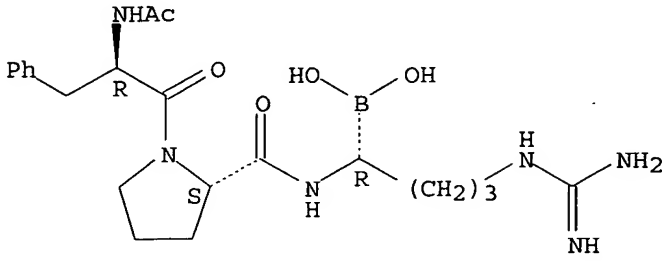
AB Anticoagulants are directed to clots by conjugating them with ligands for clot proteins such as an antibody to fibrin. The clot-targeting, anticoagulant mol. may also include a thrombolytic coupled to the clot-targeting binding mol. or a thrombolytic coupled to the anticoagulant. Conjugates of the Fab-SH fragment of anti-thrombin antibody DD-3B6/22 and the anticoagulant peptide PPACK were prepared by standard methods. The conjugate was able to bind thrombin and the D-dimer and to inhibit thrombin action in a dose-dependent manner. The chemical synthesis of conjugates of the antibody and hirudin analogs and the cloning of genes for antibody fragments for preparation of conjugates by expression of cloned genes for fusion proteins are described.

IT **130982-43-3DP**, DuP 714, conjugates with antibodies to clot components
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as anticoagulants)

RN 130982-43-3 HCAPLUS

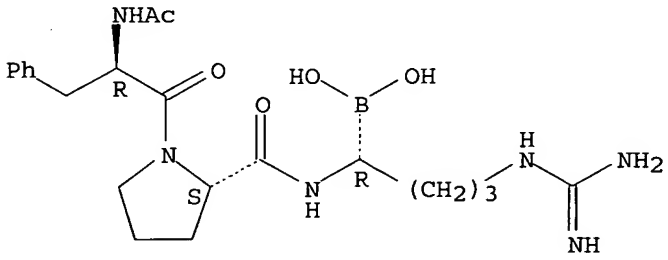
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 45 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:465651 HCAPLUS
DOCUMENT NUMBER: 121:65651
TITLE: Analysis of diastereoisomer impurities in chiral pharmaceutical compounds by capillary electrophoresis
AUTHOR(S): Williams, R. C.; Edwards, J. F.; Ainsworth, C. R.
CORPORATE SOURCE: DuPont Merck Pharm. Co., Wilmington, DE, 19880-0353, USA
SOURCE: Chromatographia (1994), 38(7-8), 441-6
CODEN: CHRGB7; ISSN: 0009-5893
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Micellar electrokinetic capillary chromatog. (MECC) was applied to the separation and anal. of diastereoisomer impurities in chiral pharmaceutical compds. Differences in separation mechanism and selectivity make MECC useful as an alternative method to HPLC for anal. of these synthetic impurities. Advantages of MECC include high efficiency sepns. and low consumption of sample and solvents. Water soluble and insol. pharmaceutical compds. are used to illustrate the separation characteristics and quant. capabilities of this versatile new anal. technique.
IT **130982-43-3 156475-60-4**, JCR 101
RL: PROC (Process)
(separation of, by micellar electrokinetic capillary chromatog.)
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

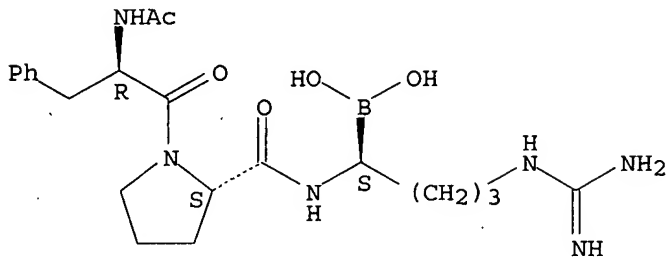
Absolute stereochemistry.



RN 156475-60-4 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1S)-4-[(aminoiminomethyl)amino]-

1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



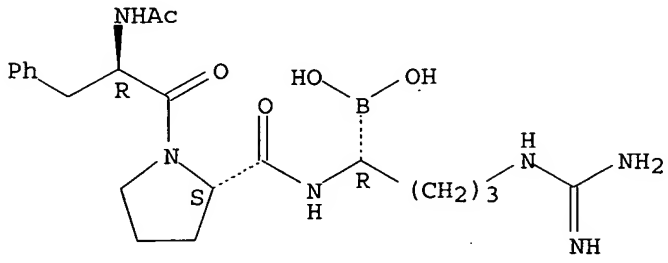
L13 ANSWER 46 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:289774 HCAPLUS
DOCUMENT NUMBER: 120:289774
TITLE: Fibrinolytic compromise by simultaneous administration of site-directed inhibitors of thrombin
AUTHOR(S): Callas, Demetra; Bacher, Peter; Iqbal, Omer; Hoppensteadt, Debra; Fareed, Jawed
CORPORATE SOURCE: Stritch Sch., Loyola Univ., Chicago, Maywood, IL, USA
SOURCE: Thrombosis Research (1994), 74(3), 193-205
CODEN: THBRAA; ISSN: 0049-3848
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Newly developed synthetic and recombinant thrombin inhibitors possess strong anticoagulant effects. Despite these effects, interactions of these agents with enzymes in the fibrinolytic network result in the modulation of such proteases as t-PA, u-PA and streptokinase. The inhibitory spectrum of several thrombin inhibitors [D-Phe-Pro-Arg-H (GYKI 14166), D-MePhe-Pro-Arg-H (GYKI 14766), Boc-D-Phe-Pro-Arg-H (GYKI 14451), Ac-D-Phe-Pro-boroArg-OH (DuP 714), recombinant hirudin (r-Hir) and unfractionated porcine mucosal heparin complexed with antithrombin III (Heparin/AT-III)] was studied towards various serine proteases such as tissue plasminogen activator (t-PA), plasmin, plasminogen/streptokinase complex, urokinase and kallikrein. Aprotinin was also studied in the same systems as the thrombin inhibitors. All four tripeptide derivs. were found to inhibit t-PA, plasmin and plasminogen/streptokinase complex at micromolar concns. (IC50: 0.57 mM - 3.3 μM). Boc-D-Phe-Pro-Arg-H and Ac-D-Phe-Pro-boroArg-OH also inhibited urokinase, while Ac-D-Phe-Pro-boroArg-OH inhibited kallikrein as well (IC50: 0.15 mM - 16 μM). In contrast, r-Hir and Heparin/AT-III did not inhibit any of these enzymes at millimolar concns. (IC50 ≥ 1 mM). Aprotinin inhibited plasmin, plasminogen/streptokinase complex and kallikrein at micromolar concns. (IC50: 3.1-0.85 μM). In a rabbit thrombolysis model, where pre-formed clots are lysed by streptokinase, simultaneous administration of D-MePhe-Pro-Arg-H or Ac-D-Phe-Pro-boroArg-OH, at concns. .apprx.1 μmol/kg, I.V. resulted in complete inhibition of the fibrinolytic process. Aprotinin at 0.1 μmol/kg, I.V. produced similar inhibition. These results demonstrate that thrombin inhibitors may exert significant antiprotease actions against various fibrinolytic enzymes.

IT **130982-43-3**, DuP 714
RL: BIOL (Biological study)
(thrombin inhibitor, serine protease inhibitory activity of, fibrinolytic compromise in relation to)
RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 47 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:261361 HCAPLUS
DOCUMENT NUMBER: 120:261361
TITLE: Use of a direct inhibitor of thrombin for the production of a drug with thrombolytic activity
INVENTOR(S): Berry, Christopher; Ferrari, Patrice
PATENT ASSIGNEE(S): Synthelabo S. A., Fr.
SOURCE: Eur. Pat. Appl., 6 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 589741	A1	19940330	EP 1993-402136	19930902
EP 589741	B1	19980311		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
FR 2695562	A1	19940318	FR 1992-10833	19920911
FR 2695562	B1	19941014		
AT 163856	E	19980315	AT 1993-402136	19930902
ES 2115741	T3	19980701	ES 1993-402136	19930902
CA 2105888	AA	19940312	CA 1993-2105888	19930910
NO 9303235	A	19940314	NO 1993-3235	19930910
AU 9346281	A1	19940317	AU 1993-46281	19930910
ZA 9306707	A	19940330	ZA 1993-6707	19930910
CN 1087015	A	19940525	CN 1993-117197	19930910
CN 1066961	B	20010613		
JP 06228007	A2	19940816	JP 1993-225606	19930910
IL 106981	A1	19990312	IL 1993-106981	19930910
US 5583113	A	19961210	US 1995-387382	19950213
PRIORITY APPLN. INFO.:			FR 1992-10833 A	19920911
			US 1993-114067 B1	19930831

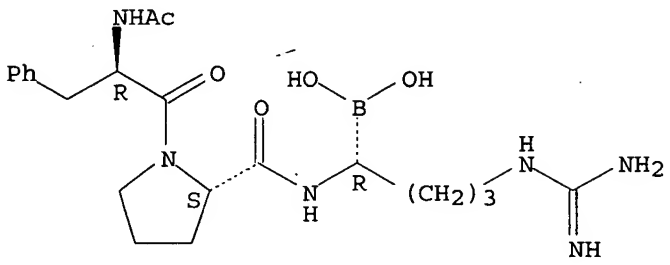
AB Direct inhibitors of thrombin are used for the production of a drug with thrombolytic activity. The thrombolytic effect of 25-200μg argatroban/kg was shown in rats.

IT **130982-43-3**, Dup 714
RL: BIOL (Biological study)
(as thrombolytic agent)

RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-

1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

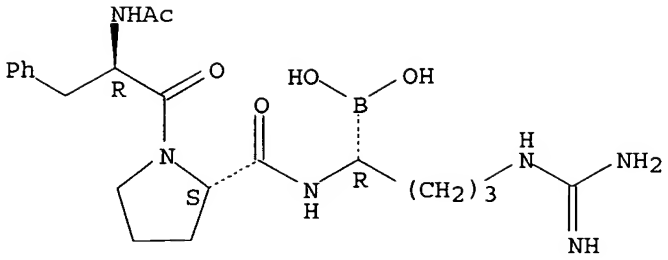


L13 ANSWER 48 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:208253 HCAPLUS
DOCUMENT NUMBER: 120:208253
TITLE: Comparative studies on the inhibitory spectrum of recombinant hirudin, DuP 714 and heparin on thrombin and factor Xa generation in biochemically defined systems
AUTHOR(S): Kaiser, B.; Callas, D.; Hoppensteadt, D.; Mallinowska, K.; Fareed, J.
CORPORATE SOURCE: Med. Cent., Loyola Univ., Maywood, IL, 60153, USA
SOURCE: Thrombosis Research (1994), 73(5), 327-35
CODEN: THBRAA; ISSN: 0049-3848
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of antithrombotic drugs on the generation of serine proteases was studied in a biochem. defined system in which the prothrombin complex concentrate Konyne provided the necessary coagulation factors in the absence of plasma. The amount of thrombin and factor Xa generation was measured with a chromogenic substrate on a microcentrifugal analyzer. Furthermore, the assay was modified by supplementation with either purified antithrombin III or factor V. Of the 3 title compds., the synthetic peptide DuP 714 was the most effective inhibitor of thrombin, and it also had strong inhibitory actions against factor Xa generation. Recombinant hirudin (rH) was nearly as active as DuP 714 on thrombin generation; however, it was less effective on factor Xa generation. With rH no concentration-dependent inhibition of factor Xa generation was found: over a wide range of concentration
it produced a steady inhibition of only 40-50% without further increase. The addition of antithrombin III to the system did not influence the action of DuP 714 or rH, but it strongly increased the inhibitory effects of unfractionated heparin as well as of a low-mol.-weight heparin on both thrombin and factor Xa generation. The addition of factor V to the assay system did not change the activity of any of the agents on protease generation.

IT **130982-43-3**, DuP 714
RL: BIOL (Biological study)
(blood-coagulation factor Xa and thrombin generation inhibition by)
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



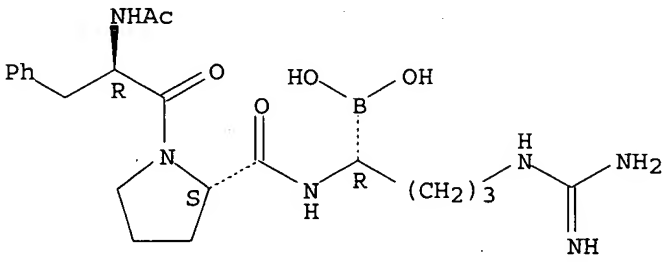
L13 ANSWER 49 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:182712 HCAPLUS
DOCUMENT NUMBER: 120:182712
TITLE: Investigation of a thrombin inhibitor peptide as an alternative to heparin in cardiopulmonary bypass surgery
AUTHOR(S): Chomiak, Paul N.; Walenga, Jeanine M.; Koza, Michael J.; Reilly, Thomas M.; Turlapathy, Prasad; Pifarre, Roque
CORPORATE SOURCE: Med. Cent., Loyola Univ., Maywood, IL, 60153, USA
SOURCE: Circulation (1993), 88(5, Pt. 2), 407-12
CODEN: CIRCAZ; ISSN: 0009-7322
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study was undertaken to determine if a newly developed synthetic peptide thrombin inhibitor (DuP 714; DuPont-Merck, Wilmington, Del) could be used as an anticoagulant in cardiopulmonary bypass (CPB) surgery. Anesthetized mongrel dogs were placed on CPB for 1 h and then observed for 2 h. Following a dose-finding study, the optimal dose (DuP 714 group) and an overdose (DuP-HI group) were studied. The DuP 714 group received 0.25 mg/kg IV bolus plus 0.5 mg/kg/h infusion of DuP 714 and the DuP-HI group received 0.5 mg/kg IV bolus plus 1.0 mg/kg/h infusion of DuP 714. No neutralizing agent was used. The control group received 2.0 mg/kg intracardiac bolus of heparin with 0.15 mg/kg IV bolus injections as needed to maintain the activated clotting time (ACT) at >300 s during CPB. Protamine sulfate (2.0 mg/kg) was used to reverse heparin after CPB. Postoperative blood loss for both DuP 714 groups was less than that for heparin (177 and 297 vs. 318 g, P=NS). The DuP 714 group revealed higher pump line filter fibrin deposits (15.5 mg, ANOVA) compared with the heparin group (4.2 mg), whereas the DuP-HI group showed equivalent deposits (9.3 mg). The ACT levels recorded during and 30 min after CPB were 638 and 160 s in the DuP 714 group and >800 and 436 s in the DuP-HI group; however, the ACT level only in the DuP-HI group remained elevated 2 h after CPB. Platelet counts were significantly higher in both DuP 714 groups after CPB. There was nearly complete elimination of all peptide in the urine. No statistical difference was observed in hemodynamics (cardiac index and systemic vascular resistance) in any of the groups. This study reveals that the peptide inhibitor DuP 714 can effectively function as an anticoagulant in a canine CPB model. The efficacy and safety, even when overdosed, are demonstrated by reduced blood loss and lack of platelet count reduction Clin. monitoring can be achieved by the use of ACT levels. No evidence of hemodynamic compromise was noted with the drug administration.

IT **130982-43-3**, DuP 714
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticoagulant activity of, in cardiopulmonary bypass surgery)

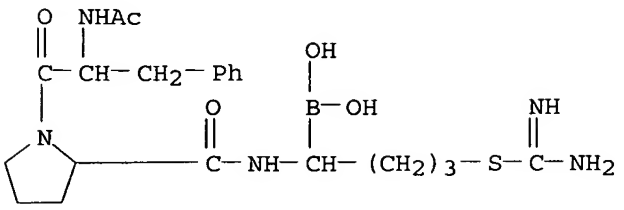
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



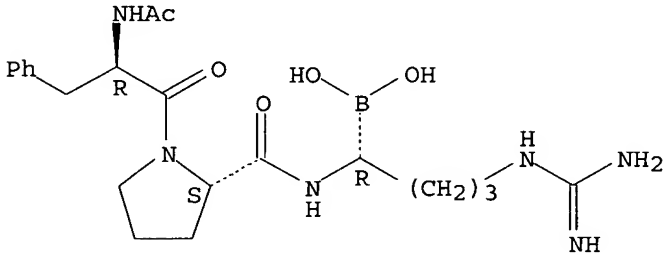
L13 ANSWER 50 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:534092 HCAPLUS
DOCUMENT NUMBER: 119:134092
TITLE: The solution conformation of (D)Phe-Pro-containing peptides: implications on the activity of Ac-(D)Phe-Pro-boroArg-OH, a potent thrombin inhibitor
AUTHOR(S): Lim, Marguerita S. L.; Johnston, Eric R.; Kettner, Charles A.
CORPORATE SOURCE: Du Pont Merck Pharm. Co., Wilmington, DE, 19880-0328, USA
SOURCE: Journal of Medicinal Chemistry (1993), 36(13), 1831-8
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ac-(D)Phe-Pro-boroArg-OH is a potent, competitive inhibitor of thrombin (Ki = 40 pM). 1H-NMR studies have shown that the peptide portion, -(D)Phe-Pro-, has secondary structure in aqueous solns. This structure corresponds fairly closely to the structure of H-(D)Phe-Pro-ArgCH2Cl complexed to thrombin in the protein crystal structure (Bode, W.; et al., 1989). These results indicate that, in addition to enthalpic interactions in the active site of the enzyme, there are significant entropic advantages in binding this mol. not previously recognized. It is estimated that they contribute .apprx.10-fold to binding. The structure observed can be explained by π-π interactions between the Ph side chain of (D)Phe and the (D)Phe-Pro peptide bond. Assignment of structure is based first on the 0.8-1.2 ppm difference between the two Pro Cδ protons. The magnitude of these chemical shifts are consistent with aromatic ring current-induced effects expected for distances in the structure. The structure was further defined by interproton distances and correlation times calculated by backtransformation and correction of the NOESY and ROESY data to the longitudinal and transverse cross relaxation rates. Anal. of the vicinal coupling consts. show that Pheχ1 is not fixed. Correlation times for the peptide side chains and backbone indicate that the Ph ring and boroArg side chain possess various degrees of internal motion, and that the rest of the peptide has a fairly rigid conformation.
IT **149730-92-7**
RL: BIOL (Biological study)
(NMR assignment of, D-phenylalanylproline moiety secondary structure in relation to)
RN 149730-92-7 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[4-[(aminoiminomethyl)thio]-1-

boronobutyl]-, (R)- (9CI) (CA INDEX NAME)



IT **130982-43-3**
RL: BIOL (Biological study)
(secondary structure of D-phenylalanylproline moiety of, thrombin inhibition in relation to)
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 51 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1993:73409 HCAPLUS
DOCUMENT NUMBER: 118:73409
TITLE: Effect of thrombin inhibitors on platelet functions: comparative analysis of DuP 714 and hirudin
AUTHOR(S): Reilly, T. M.; Knabb, R. M.; Hassell, S. M.; Bozarth, J. M.; Forsythe, M. S.; Mayo, M. C.; Racanelli, A. L.; Mousa, S. A.
CORPORATE SOURCE: Exp. Stn., Du Pont Merck Pharm. Co., Wilmington, DE, 19880-0400, USA
SOURCE: Blood Coagulation & Fibrinolysis (1992), 3(5), 513-17
CODEN: BLFIE7; ISSN: 0957-5235
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Since thrombin plays an important role in platelet-mediated arterial thrombosis, we have examined the antiplatelet activity of a synthetic thrombin inhibitor, DuP 714 (Ac-(D)Phe-Pro-boroArg), in comparison with that of the naturally occurring inhibitor hirudin. Hirudin was slightly more potent than DuP 714 in inhibiting thrombin-induced aggregation in washed human platelets (IC50s of 72 nM and 150 nM, resp.) and in inhibiting the secretion of plasminogen activator inhibitor-I from human platelets (IC50s of 300 nM and 900 nM, resp.). In contrast, DuP 714 was more potent than hirudin in inhibiting thrombin-induced [125I]fibrinogen binding to gel purified platelets, and in inhibiting thrombin-induced intracellular calcium mobilization in washed platelets. These results

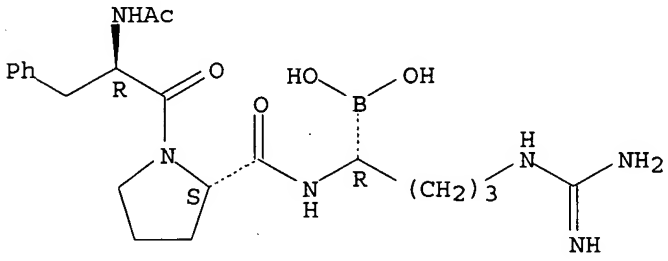
indicate that the tripeptide DuP 714 has comparable antiplatelet activity to the 65 amino acid hirudin. We conclude that DuP 714 may have clin. utility in the prevention of platelet-dependent, arterial thrombotic processes.

IT **130982-43-3**, DuP 714
RL: BIOL (Biological study)
(platelet function response to, anticoagulant activity in relation to)

RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 52 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1993:545 HCAPLUS

DOCUMENT NUMBER: 118:545

TITLE: Prevention of thrombus growth by antithrombin III-dependent and two direct thrombin inhibitors in rabbits: implications for antithrombotic therapy

AUTHOR(S): Brill-Edwards, Patrick; Van Ryn-McKenna, Joanne; Cai, Lu; Ofosu, Frederick A.; Buchanan, Michael R.

CORPORATE SOURCE: Med. Cent., McMaster Univ., Hamilton, ON, Can.

SOURCE: Thrombosis and Haemostasis (1992), 68(4), 424-7
CODEN: THHADQ; ISSN: 0340-6245

DOCUMENT TYPE: Journal

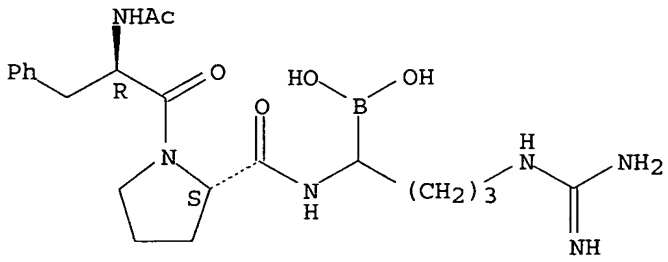
LANGUAGE: English

AB The authors compared the abilities of heparin and two direct thrombin inhibitors to prevent fibrin accretion onto pre-existing thrombi in rabbits. Inhibition of thrombus growth was measured as the ability of each test compound to inhibit the accretion of 125I-fibrin onto thrombi pre-formed in jugular veins of rabbits. When administered as a continuous infusion, the two direct (i.e. antithrombin III-independent) thrombin inhibitors, r-hirudin and a tripeptide, Ac(D)-Phe-Pro-bor-Arg (P-8714) inhibited fibrin accretion as effectively as heparin, but did so in doses which generated little systemic anticoagulation, as compared to the marked anticoagulation associated with the heparin effect. However, both r-hirudin and P-8714 were more effective when they were administered as a single bolus injection than as a continuous infusion. Under the former conditions, there was only a transient systemic anticoagulant effect. Thus, direct or antithrombin III-independent thrombin inhibitors are more effective than heparin in preventing thrombus growth. The limited effect of heparin is likely due to fibrin impairing the ability of heparin/antithrombin III to inactivate thrombin.

IT **124216-70-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antithrombotic activity of, compared to heparin)

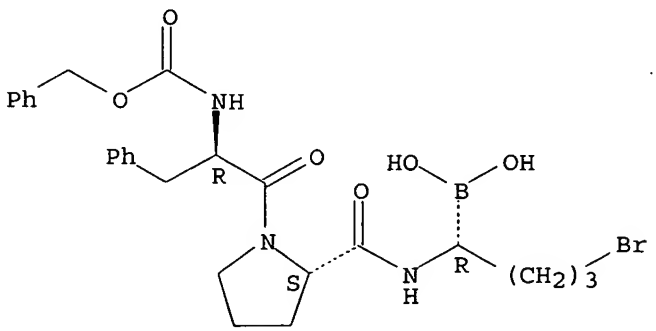
RN 124216-70-2 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

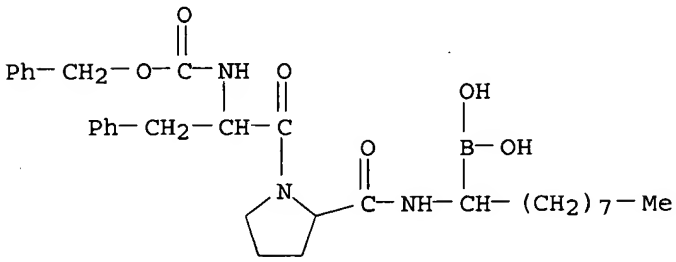


L13 ANSWER 53 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1992:572073 HCAPLUS
DOCUMENT NUMBER: 117:172073
TITLE: New peptide boronic acid inhibitors of thrombin
AUTHOR(S): Elgendy, Said; Deadman, John; Patel, Geeta; Green, Donovan; Chino, Naoyoshi; Goodwin, Christopher A.; Scully, Michael F.; Kakkar, Vijay V.; Claeson, Goran
CORPORATE SOURCE: Thrombosis Res. Inst., London, SW3 6LR, UK
SOURCE: Tetrahedron Letters (1992), 33(29), 4209-12
CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Synthetic peptides PhCH2O2C-D-Phe-Pro-NHCHRB(OR1)2 [R = (CH2)3SC(NH2):NH2+, (CH2)3OMe, (CH2)4Me, CMe2Et, CH2Ph, (CH2)3Br, (CH2)7Me, 2-(2-dioxolanyl)ethyl; (OR1)2 = pinanediol diester, pinacol diester] containing a P1 aminoboronic acid with a neutral side chain show good thrombin inhibition as well as selectivity for thrombin, and have no serious side effect on blood pressure.
IT **143718-39-2DP**, pinanediol or pinacol diesters
143718-40-5DP, pinanediol or pinacol diesters
143718-41-6DP, pinanediol or pinacol diesters
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and thrombin inhibitory activity of)
RN 143718-39-2 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1R)-1-borono-4-bromobutyl]- (9CI) (CA INDEX NAME)

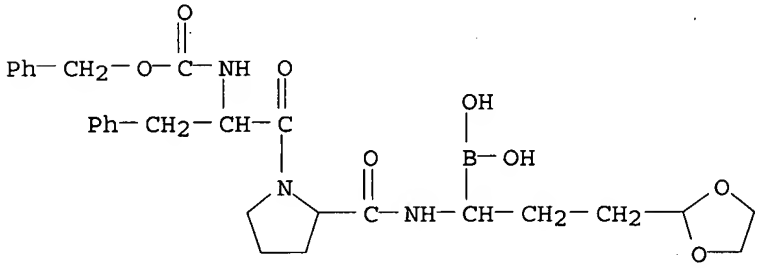
Absolute stereochemistry.



RN 143718-40-5 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-(1-boronononyl)-, (R)- (9CI) (CA INDEX NAME)



RN 143718-41-6 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[1-borono-3-(1,3-dioxolan-2-yl)propyl]-, (R)- (9CI) (CA INDEX NAME)



L13 ANSWER 54 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1992:166038 HCAPLUS
DOCUMENT NUMBER: 116:166038
TITLE: In vivo characterization of a new synthetic thrombin inhibitor
AUTHOR(S): Knabb, Robert M.; Kettner, Charles A.; Timmermans, Pieter B. M. W. M.; Reilly, Thomas M.
CORPORATE SOURCE: Du Pont Merck Pharm. Co., Wilmington, DE, 19880-0400, USA
SOURCE: Thrombosis and Haemostasis (1992), 67(1), 56-9
CODEN: THHADQ; ISSN: 0340-6245
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The in vivo pharmacol. of DuP 714 (Ac-[D[-Phe-Pro-boroArginine), a representative of a new series of synthetic thrombin inhibitors which contain a boronic acid derivative of arginine, was studied. I.v. bolus injections of DuP 714 in anesthetized rats and conscious rabbits produced transient elevations of clotting times. Clin. relevant prolongations of the APTT were also observed in rabbits after i.v. infusion of less than 0.1 mg kg-1 h-1. Efficacy against venous thrombosis was demonstrated in a rabbit model of stasis induced thrombosis. Clots formed in 100% of control animals and only 33% of animals treated with 0.5 mg/kg DuP 714, and were less severe in treated animals. In a rabbit arterial venous shunt model mimicking arterial thrombosis, occlusion occurred within 30 min in 71% of control animals vs. 11% of animals treated with 0.1 mg kg-1

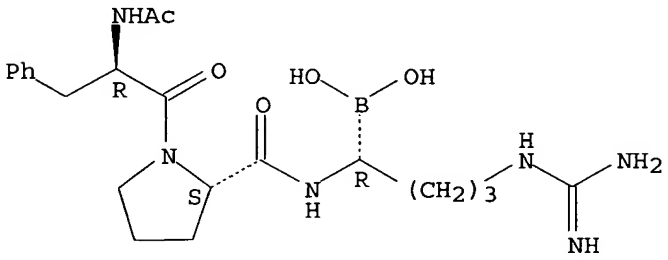
h-1 DuP 714. Results indicate that DuP 714 is a highly effective anticoagulant which should be useful for the prevention of both venous and arterial thrombotic diseases.

IT **130982-43-3**, DuP 714
RL: PRP (Properties)
(anticoagulant effects of, as thrombin inhibitor)

RN 130982-43-3 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L13 ANSWER 55 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1992:34171 HCAPLUS

DOCUMENT NUMBER: 116:34171

TITLE: Anticoagulant activity of a peptide boronic acid thrombin inhibitor by various routes of administration in rats

AUTHOR(S): Hussain, Munir A.; Knabb, Robert; Aungst, Bruce J.; Kettner, Charles

CORPORATE SOURCE: DuPont Merck Pharm. Co., Wilmington, DE, 19880-0400, USA

SOURCE: Peptides (New York, NY, United States) (1991), 12(5), 1153-4
CODEN: PPTDD5; ISSN: 0196-9781

DOCUMENT TYPE: Journal

LANGUAGE: English

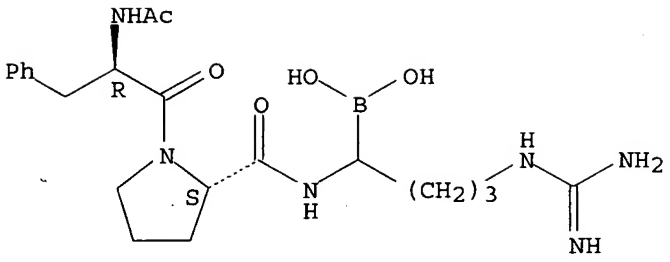
AB The peptide boronic acid analog Ac-D-Phe-Pro-boro-Arg-OH (I) is a potent and selective inhibitor of thrombin. I may be active orally or when administered by alternative transmucosal routes. The measured effect was the time for clotting of blood plasma initiation with thrombin. With this assay there was a narrow window from no measurable effect to the maximal anticoagulant effect with a clotting time >300 s. I.v. I at a 0.15 mg/kg dose in rats, a nasal 0.45 mg/kg dose, and 3 mg/kg doses administered orally, colonically, or rectally all produced maximal effects. Although bioavailability could not be estimated, this peptide analog was absorbed by each of these routes in rats.

IT **124216-70-2**
RL: BIOL (Biological study)
(anticoagulant properties of, transmucosal routes of administration effect on)

RN 124216-70-2 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

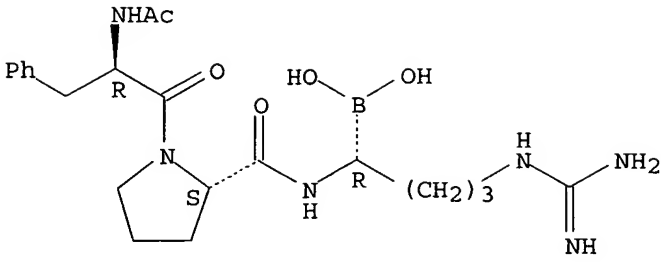


L13 ANSWER 56 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:623133 HCAPLUS
DOCUMENT NUMBER: 115:223133
TITLE: Inhibition of thrombin-platelet reactions by DuP 714
AUTHOR(S): Chiu, Andrew T.; Mousa, Shaker A.; Pease, Lori J.; Roscoe, William A.; Bozarth, Jeffrey M.; Reilly, Thomas M.; Smith, Ronald D.; Timmermans, P. B. M. W. M.
CORPORATE SOURCE: Du Pont Merck Pharm. Co., Wilmington, DE, 19880-0400, USA
SOURCE: Biochemical and Biophysical Research Communications (1991), 179(3), 1500-8
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The efficacy and specificity of a novel synthetic thrombin inhibitor, DuP 714, on thrombin-induced elevation of cytoplasmic calcium, fibrinogen binding and aggregation in human platelets were examined Thrombin (0.5 U/mL) stimulated an increase in [125I]fibrinogen binding in gel-filtered platelets which was blocked by DuP 714 with an IC50 value of 2 nM. Thrombin (1 U/mL)-induced elevation of intracellular [Ca2+]i was also blocked by DuP 714 with an IC50 value of 67 nM. A much higher concentration of thrombin (25 U/mL) was used to stimulate aggregation with heparinized platelet-rich plasma. Under these conditions, micromolar concns. of DuP 714 were needed to inhibit thrombin. In all of these prepns., DuP 714 at concns. as high as 10-5M had no intrinsic effects and did not affect the responses induced by arachidonate, ADP, collagen, epinephrine, vasopressin and serotonin. These data indicate that DuP 714 is a potent and specific thrombin inhibitor capable of arresting the actions of thrombin on human fibrin formation and platelet aggregation and secretion. It may serve as a potential antithrombotic agent for various forms of thrombotic disorders.

IT **130982-43-3**, DuP 714
RL: BIOL (Biological study)
(thrombin-induced elevation of intracellular calcium and fibrinogen binding and aggregation in human platelet inhibition by)
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

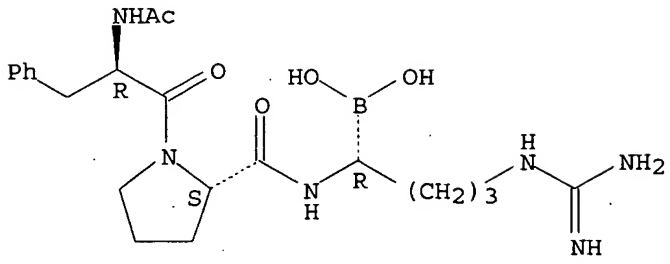


L13 ANSWER 57 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:35423 HCAPLUS
DOCUMENT NUMBER: 114:35423
TITLE: The selective inhibition of thrombin by peptides of boroarginine
AUTHOR(S): Kettner, Charles; Mersinger, Lawrence; Knabb, Robert
CORPORATE SOURCE: Mol. Biol. Div., E. I. du Pont de Nemours Co. Inc., Wilmington, DE, 19880-0328, USA
SOURCE: Journal of Biological Chemistry (1990), 265(30), 18289-97
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peptides containing α-aminoboronic acids with neutral side chains are highly effective reaction intermediate analog inhibitors of the serine proteases leukocyte elastase, pancreatic elastase, and chymotrypsin. A protocol was developed for the synthesis of peptides containing α-aminoboronic acids with a basic, 3-guanidinopropyl side chain (boroArg) to extend the range of these compds. to trypsin-like proteases. Ac-(D)Phe-Pro-boroArg-OH, Boc-(D)Phe-Pro-boroArg-OH, and H-(D)Phe-Pro-boroArg-OH were prepared as inhibitors of thrombin, based on earlier observations that it has a high affinity for this sequence. All 3 boronic acids are highly effective, slow-binding inhibitors of thrombin, inhibiting it with final inhibition consts. and association rates of 41 pM, 5.5 + 106 M-1 s-1; 3.6 pM, 9.3 + 106 M-1 s-1; <1 pM, 8.0 + 106 M-1 s-1, resp. Comparison of their binding at equilibrium to thrombin, plasma kallikrein, factor Xa, plasmin, and 2-chain tissue plasminogen activator has shown that all 3 inhibitors have at least 2 orders of magnitude greater affinity for thrombin, with the exception of the acetyl derivative which has a 40-fold greater affinity for thrombin than kallikrein. The boroarginine peptides are effective in inhibiting the action of thrombin in rabbit plasma against its physiol. substrates. Activated partial thromboplastin time was significantly prolonged in vitro by all of the inhibitors at concns. of 50-200 nM. Prolongations of activated partial thromboplastin time were also observed in rabbits after i.v. (40-80 μg/kg) or s.c. (0.20-2 mg/kg) injections of Ac-(D)Phe-Pro-boroArg-OH. Results indicate that this new class of synthetic thrombin inhibitors may be clin. useful as antithrombotic agents.

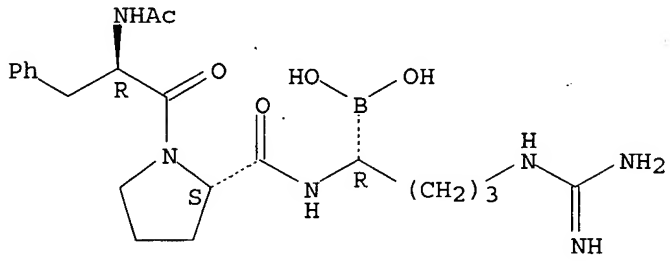
IT **130982-43-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and thrombin inhibition by, antithrombotic activity in relation to)
RN 130982-43-3 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **131062-98-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 131062-98-1 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[(1R)-4-[(aminoiminomethyl)amino]-1-boronobutyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L13 ANSWER 58 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:91790 HCAPLUS
DOCUMENT NUMBER: 112:91790
TITLE: Peptide boronic acid inhibitors of trypsinlike proteases, their preparation and use as anticoagulants and inflammation inhibitors
INVENTOR(S): Kettner, Charles Adrian; Shenvi, Ashokkumar Bhikkappa
PATENT ASSIGNEE(S): du Pont de Nemours, E. I., and Co., USA
SOURCE: Eur. Pat. Appl., 61 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 293881	A2	19881207	EP 1988-108817	19880601
EP 293881	A3	19900530		
EP 293881	B1	19930310		

R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE

US 5187157	A	19930216	US 1988-178368		19880406
CA 1328332	A1	19940405	CA 1988-568224		19880531
AT 86628	E	19930315	AT 1988-108817		19880601
ES 2046237	T3	19940201	ES 1988-108817		19880601
DK 8803044	A	19881206	DK 1988-3044		19880603
FI 8802638	A	19881206	FI 1988-2638		19880603
FI 97297	B	19960815			
FI 97297	C	19961125			
NO 8802472	A	19881206	NO 1988-2472		19880603
AU 8817332	A1	19881208	AU 1988-17332		19880603
AU 623592	B2	19920521			
JP 01063583	A2	19890309	JP 1988-135770		19880603
JP 07030090	B4	19950405			
HU 49629	A2	19891030	HU 1988-2899		19880603
HU 205141	B	19920330			
ZA 8803953	A	19900228	ZA 1988-3953		19880603
IL 86613	A1	19930404	IL 1988-86613		19880603
SU 1807988	A3	19930407	SU 1988-4356026		19880603
CA 1333208	A1	19941122	CA 1991-616134		19910816
CA 1339897	A1	19980602	CA 1991-616135		19910816
RU 2017749	C1	19940815	RU 1991-5010164		19911128
US 5242904	A	19930907	US 1992-848296		19920309
US 5250720	A	19931005	US 1992-852023		19920309
PRIORITY APPLN. INFO.:			US 1987-59670	A	19870605
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			CA 1988-568224	A3	19880531
			EP 1988-108817	A	19880601

OTHER SOURCE(S): MARPAT 112:91790

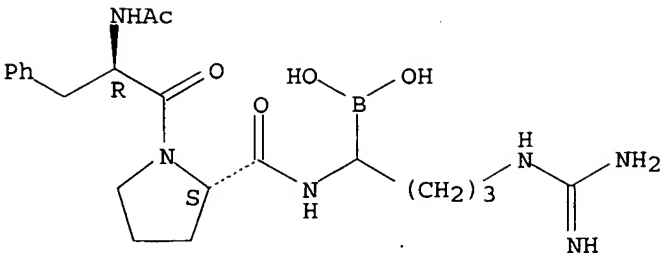
AB Peptides containing C-terminal boronic acid derivs. of lysine, ornithine, arginine, or homoarginine and corresponding isothiuronium analogs are reversible inhibitors of trypsinlike serine proteases such as thrombin, plasma kallikrein, and plasmin and are useful in treatment of blood coagulation disorders and inflammation. The peptides have the structure R1(A3qA2pA1o)nNHCHR2BY1Y2 (Y1, Y2 = OH, F; or Y1Y2 = dihydroxy compound moiety; R1 = peptide of 1-20 residues, C1-20 acyl or sulfonyl, H, N-terminal protecting group; A1-A3 = L- or D-amino acid; R2 = substituted alkyl; n, o, p, q = 0, 1) (I). In rats given Ac-D-Phe-boro-Arg (II) (where boro-Arg has a boronic acid moiety in place of CO2H) orally at 1 mg, the blood clotting time (thrombin time) was increased to >300 s for 3 h (control, 34 s). II-HCl at 5 nm inhibited the activity of human thrombin (1.0 nM) by 97% in vitro (initial substrate concentration 0.10 mM). Allyl bromide was hydroborated with catechol borane, transesterified with (+)-α-pinanediol, homologated, and aminated to yield 1-amino-4-bromobutyl boronate pinanediol.HCl, which was coupled to Boc-D-Phe-Pro (Boc = tert-butoxycarbonyl) (preparation given) and converted in 5 addnl. steps to II-HCl.

IT **124215-57-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as protease inhibitor)

RN 124215-57-2 HCAPLUS

CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-boronobutyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

IT **124216-70-2**
RL: BIOL (Biological study)
(protease inhibition by)
RN 124216-70-2 HCAPLUS
CN L-Prolinamide, N-acetyl-D-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-boronobutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.